Case/Application number: 10/571,734
Additional comments:
The elected species have been indicated in the attachment. Only claims 2, 6 and 11-13 are presented for examination. I have also included an excerpt of the claims representing the claims under examination for clarity.

The Examiner has requested a species for examination purposes. Applicants elect the histone deacetylase inhibitor, *N*-hydroxy-3-[4-{[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl}phenyl]-2*E*-2-propenamide and the death receptor ligand, TRAIL/Apo-2L.

2. (original) A method for the prevention or treatment of proliferative diseases, in a mammal, which comprises treating the mammal with pharmaceutically effective amounts of a combination of:

(a) death receptor ligand, and

(b) a histone deacetylase inhibitor of formula (i) according to claim 1.

6. (original) The method of Claim 2, wherein the mammal is a human.

11. (original) A method of treating or preventing premalignant proliferative diseases in a mammal which comprises treating the mammal with a combination of:

(a) a pharmaceutically effective amount of a death receptor ligand; and

(b) a pharmaceutically effective amount of *N*-hydroxy-3-[4-{[(2-hydroxyethyl)[2-(*1H*-indol-3-yl)ethyl]-amino]methyl}phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-{[[2-(*1H*-indol-3-yl)ethyl]-amino]methyl}phenyl]-2*E*-2-propenamide or *N*-hydroxy-3-[4-[[2-(2-methyl-*1H*-

```
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DICTIONARY FILE UPDATES:  18 AUG 2008  HIGHEST RN 1041768-00-6

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L1      4222979 S ?HYDROXY?/CNS
L2       259102 S ?PROPENAMIDE?/CNS
L3       262916 S ?"INDOL-3-YL"?/CNS
L4          711 S L1(L)L2(L)L3
                E "APO-2L"/CN
                E TRAIL/CN
L5           12 S E3-E14

                E HISTONE DEACETYLASE/CN
L7          195 S HISTONE DEACETYLASE?/CN

                E "CASPASE-8"/CN 5
L46          14 S "CASPASE-8"?/CN

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FILE COVERS 1907 - 19 Aug 2008  VOL 149 ISS 8
FILE LAST UPDATED: 18 Aug 2008  (20080818/ED)

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2008.
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This file contains CAS Registry Numbers for easy and accurate substance identification.

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L1      4222979 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?HYDROXY?/CNS
L2       259102 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?PROPENAMIDE?/CNS
L3       262916 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?"INDOL-3-YL"?/CNS
L4          711 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1(L)L2(L)L3
L5           12 SEA FILE=REGISTRY ABB=ON  PLU=ON  (TRAIL/CN OR "TRAIL
                (TUMOR NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND)
                (52-ASPARAGINE, 82-GLUTAMINE) (HUMAN)"/CN OR "TRAIL (TUMOR
                NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND) (HUMAN
                FRAGMENT)"/CN OR "TRAIL RECEPTOR 1/TR4 (HUMAN)"/CN OR
                "TRAIL RECEPTOR 2 (HUMAN CELL LINE NTERA-2)"/CN OR "TRAIL
                RECEPTOR 2 (HUMAN GENE DR5)"/CN OR "TRAIL RECEPTOR 2/TR7
                (HUMAN)"/CN OR "TRAIL RECEPTOR 3 (HUMAN)"/CN OR "TRAIL
                RECEPTOR 3/TR5 (HUMAN)"/CN OR "TRAIL RECEPTOR 4/TR10
                (HUMAN)"/CN OR "TRAIL RECEPTOR APO-2 (357-LEUCINE) (HUMAN
                CLONE 27868 PRECURSOR)"/CN OR "TRAIL RECEPTOR APO-2
                (357-METHIONINE) (HUMAN CLONE 27868 PRECURSOR)"/CN)
L6             9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (HYDROXY(S)INDOL?)(S)(2(W)
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L7           195 SEA FILE=REGISTRY ABB=ON  PLU=ON  HISTONE DEACETYLASE?/CN
L8         12435 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR L6 OR L7 OR HDAI OR
                HDAC OR HDI OR HISTONE(W)(DEACETYLASE OR DE ACETYLASE)
L9         32923 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 OR DR4 OR DR5 OR
                (DECOY OR DEATH)(W)RECEPTOR OR DCR2 OR DCR 2 OR TRAIL OR
                APO2L OR APO2 OR (APO OR APOPTOS? OR APOPTOT?)(W)(2 OR 2L)
                OR AGONIST?(3A)ANTIBOD? OR (TNF OR (TUMOUR OR TUMOR)(W)NECR
                OSIS)(5A)(LIGAND OR SUPERFAMIL? OR SUPER FAMIL? OR
                RECEPTOR)
L10          136 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8(L)L9
L38       274695 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (TREAT? OR THERAP? OR
                PREVENT?)(S)((PROLIFERAT? OR PRO LIFERAT?)(3A)(DISEAS? OR
                DISORDER) OR ?CANCER? OR ?CARCIN? OR ?TUMOUR? OR ?TUMOR?
                OR ?NEOPLAS? OR AML OR LEUKEMI## OR LEUKAEMI##)
L39           77 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10(L)L38
L40           31 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39(L)(MAMMAL? OR HUMAN)


L1      4222979 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?HYDROXY?/CNS
L2       259102 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?PROPENAMIDE?/CNS
L3       262916 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?"INDOL-3-YL"?/CNS
L4          711 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1(L)L2(L)L3
L6            9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (HYDROXY(S)INDOL?)(S)(2(W)
                PROPENAMIDE)
L7           195 SEA FILE=REGISTRY ABB=ON  PLU=ON  HISTONE DEACETYLASE?/CN
L8         12435 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR L6 OR L7 OR HDAI OR
                HDAC OR HDI OR HISTONE(W)(DEACETYLASE OR DE ACETYLASE)
L12         8819 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "CYTOKINE RECEPTORS"+OLD/C
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L13       318585 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ANTIBODIES AND IMMUNOGLOB
                ULINS"+OLD,PFT/CT
L14          478 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND (L13 OR L12)
L15          353 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND HUMAN/CT
L16       272881 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ANTITUMOR AGENTS"+OLD,PFT
                /CT
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L17      193859 SEA FILE=HCAPLUS ABB=ON  PLU=ON  NEOPLASM+OLD,PFT/CT
L18       41140 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LEUKEMIA+OLD,PFT/CT
L19        9985 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ACUTE MYELOID LEUKEMIA"+O
                LD,PFT/CT
L20        2538 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "DISEASE, ANIMAL (L)
                PROLIFERATIVE"+OLD,PFT/CT
L21         219 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND ((L16 OR L17 OR
                L18 OR L19 OR L20))
L22      199042 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "SIGNAL TRANSDUCTION"+OLD,
                PFT/CT
L23       16484 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "CYCLIN DEPENDENT KINASE
                INHIBITORS"+PFT/CT
L24      125051 SEA FILE=HCAPLUS ABB=ON  PLU=ON  APOPTOSIS+OLD,PFT/CT
L41          91 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 AND L24
L42          30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41 AND (L22 OR L23)
L43          30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L42 AND HUMAN/CT
L44          30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L43 AND THU/RL
L46          14 SEA FILE=REGISTRY ABB=ON  PLU=ON  "CASPASE-8"?/CN
L48          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L44 AND (L46 OR (CASP OR
                CASPASE)(1W)8 OR FLICE OR (MACH OR MCH5 OR MCH 5)(3A)(PROTE
                ASE OR PROTEINASE))

L58          39 S L40 OR L48
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L58 ANSWER 1 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 14 Aug 2008

ACCESSION NUMBER: 2008:976527 HCAPLUS Full-text
TITLE: Sp1-Mediated TRAIL Induction in Chemosensitization
AUTHOR(S): Xu, Jing; Zhou, Jun-Ying; Wei, Wei-Zen; Philipsen, Sjaak; Wu, Gen Sheng
CORPORATE SOURCE: Program in Molecular Biology and Genetics, Department of Pathology, and Program in Breast Cancer, Department of Immunology and Microbiology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA
SOURCE: Cancer Research (2008), 68(16), 6718-6726
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The regulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in cancer chemotherapy is not fully understood. Here, we show that the histone deacetylase (HDAC) inhibitors induce TRAIL in human breast cancer cells. Induction of TRAIL by the HDAC inhibitor MS275 can be enhanced by Adriamycin. Using different reporter constructs in conjunction with transcription activity assays and chromatin immunopptn. assays, we provide evidence that the transcription factor Sp1 is responsible for TRAIL induction by MS275 alone or in combination with Adriamycin. Further, we show that the combined treatment of breast cancer cells with MS275 and Adriamycin significantly increases apoptotic cell death via the activation of both death receptor and mitochondrial apoptotic pathways. Down-regulation of TRAIL by small interfering RNA silencing decreased MS275-mediated Adriamycin-induced caspase activation and apoptosis, thus conferring Adriamycin resistance. More importantly, breast cancer T47D cells in which Sp1 was knocked down or Sp1-knockout mouse embryonic stem cells were resistant to the combined treatments. Taken together, our results indicate that induction of TRAIL by the combined treatments with MS275 and Adriamycin is mediated by Sp1 and suggest that transcription factor Sp1 is an important target for the development of novel anticancer agents. [Cancer Res 2008;68(16):6718-26].

L58 ANSWER 2 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 26 May 2008
ACCESSION NUMBER: 2008:623210 HCAPLUS Full-text
DOCUMENT NUMBER: 149:143383
TITLE: Valproic acid sensitives K562 erythroleukemia cells to TRAIL/Apo2L-induced apoptosis
AUTHOR(S): Iacomino, Giuseppe; Medici, Maria Cristina; Russo, Gian Luigi
CORPORATE SOURCE: Institute of Food Sciences, National Research Council, Avellino, Italy
SOURCE: Anticancer Research (2008), 28(2A), 855-864
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Selectively targeting death receptors to trigger apoptosis in cancer cells appears ideal in cancer therapy. The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L) is of great interest since it has been shown to predominantly kill cancer cells without toxic effects on normal counterparts, thus representing a promising anticancer agent. However, resistance towards TRAIL/Apo2L treatment has also been described. To overcome this obstacle, co-administration of TRAIL/Apo2L plus several compds., including histone deacetylase inhibitors (HDACi), has been attempted as a strategy to restore cancer cell sensitivity to TRAIL-induced apoptosis. In recent years, the clin. application of HDACi has been largely explored for their ability to modulate gene transcription, block cell division cycle, inhibit cell proliferation, induce cellular differentiation and apoptosis. Materials and Methods: The ability of valproic acid (VPA), a well-known HDACi, to sensitize the K562 cell line, derived from a human leukemia, to TRAIL/Apo2L-mediated apoptosis was evaluated. VPA was selected since it is currently used in clin. practice and its pharmacokinetic, pharmacodynamic and bioavailability are known. Results: When applied with TRAIL /Apo2L, VPA increased cell death and caspase-3 activity by 4-fold compared to the treatment with TRAIL/Apo2L alone. VPA sensitized K562 cells to TRAIL/Apo2L -mediated apoptosis by increasing the expression of DR4 and DR5 by 3- and 14-fold resp. In addition, VPA per se, in the absence of TRAIL/Apo2L, reduced the expression of antiapoptotic factors, such as c-FLPs, associated with DISC, and Bcl-2/Bcl-XL, associated with mitochondria, acting on both extrinsic and intrinsic apoptotic pathways. Conclusion: Our results demonstrated the ability of VPA to sensitize TRAIL/Apo2L -resistant cells to apoptosis, thus providing an attractive approach for the treatment of leukemias and other proliferative malignancies.

L58 ANSWER 3 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 27 Mar 2008
ACCESSION NUMBER: 2008:374075 HCAPLUS Full-text
DOCUMENT NUMBER: 148:393618
TITLE: Modulation of TRAIL-induced apoptosis by HDAC inhibitors
AUTHOR(S): Fulda, Simone
CORPORATE SOURCE: University Children's Hospital, Ulm, 89075, Germany
SOURCE: Current Cancer Drug Targets (2008), 8(2), 132-140
CODEN: CCDTB9; ISSN: 1568-0096
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Triggering apoptosis, the cell's intrinsic death program, is a promising approach for cancer therapy. TNF-related apoptosis-inducing ligand (TRAIL), a member of the TNF superfamily of death inducing ligands, is of special interest for cancer therapy, since TRAIL has been shown to predominantly kill cancer cells, while sparing normal cells. However, since many cancers fail to undergo apoptosis in response to TRAIL treatment, TRAIL-based combination therapies have been developed for cancer-cell specific sensitization towards TRAIL. Chromatin remodelling plays an important role in gene regulation and aberrant architecture of the chromatin has been implicated in tumor formation and progression. In recent years, HDAC inhibitors (HDACI) that reverse aberrant epigenetic changes have emerged as a potential strategy to sensitize cancer cells for TRAIL-induced apoptosis. Synergistic tumor cell death has been reported in a variety of human cancers using different HDACI together with TRAIL. Here, recent advances in the understanding of the mol. events that underlie the synergistic interaction of HDACI and TRAIL are discussed as well as how this knowledge can be translated into the design of cancer-selective novel therapeutics.

REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 4 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 10 Mar 2008
ACCESSION NUMBER: 2008:298329 HCAPLUS Full-text
DOCUMENT NUMBER: 149:7046
TITLE: Histone deacetylase regulation of immune gene expression in tumor cells
AUTHOR(S): Khan, A. Nazmul H.; Tomasi, Thomas B.
CORPORATE SOURCE: Laboratory of Molecular Medicine, Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY, 14263, USA
SOURCE: Immunologic Research (2008), 40(2), 164-178
CODEN: IMRSEB; ISSN: 0257-277X
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Epigenetic modifications of chromatin, such as histone acetylation, are involved in repression of tumor antigens and multiple immune genes that are thought to facilitate tumor escape. The status of acetylation in a cell is determined by the balance of the activities of histone acetyltransferases and histone deacetylases . Inhibitors of histone deacetylase (HDACi) can enhance the expression of immunol. important mols. in tumor cells and HDACi treated tumor cells are able to induce immune responses in vitro and in vivo. Systemic HDACi are in clin. trails in cancer and also being used in several autoimmune disease models. To date, 18 HDACs have been reported in human cells and more than thirty HDACi identified, although only a few immune targets of these inhibitors have been identified. Here, we discuss the mol. pathways employed by HDACi and their potential role in inducing immune responses against tumors. We review data suggesting that selection of target specific HDACi and combinations with other agents and modalities, including those that activate stress pathways, may further enhance the efficacy of epigenetic therapies.

L58 ANSWER 5 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 26 Dec 2007
ACCESSION NUMBER: 2007:1463791 HCAPLUS Full-text
DOCUMENT NUMBER: 149:118815
TITLE: Differential response of p53 and p21 on HDAC inhibitor-mediated apoptosis in

HCT116 colon cancer cells in vitro and in vivo
AUTHOR(S): Zopf, Steffen; Neureiter, Daniel; Bouralexis, Steve; Abt, Tobias; Glaser, Keith B.; Okamoto, Kinya; Ganslmayer, Marion; Hahn, Eckhart G.; Herold, Christoph; Ocker, Matthias
CORPORATE SOURCE: Department of Medicine 1, University Hospital Erlangen, Erlangen, D-91054, Germany
SOURCE: International Journal of Oncology (2007), 31(6), 1391-1402
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the effect of a novel histone deacetylase inhibitor, A-423378.0, on the colon carcinoma cell line HCT116 and genetically modified derivs. lacking either p21cip1/waf1 or p53. HCT116 cell lines were incubated with A-423378.0 at different concns. for 3-120 h. Cell viability, proliferation and apoptosis rates were determined and verified by Western blot, detection of mitochondrial membrane potential breakdown $\Delta\psi m$, activation of caspases-3, -8 and cytokeratin 18 cleavage. A s.c. xenograft model was established in NMRI mice with daily i.p. injections of 10 mg/kg for 14 days. All 3 HCT116 cell lines responded to A-423378.0 treatment in a dose- and time-dependent manner via induction of apoptosis as measured by breakdown of $\Delta\psi m$ and BrdU incorporation. We identified that A-423378.0 induced the expression of TRAIL and TRAIL receptor, especially TRAIL-R2/hDR5, which was up-regulated in HCT116 cells after treatment with A-423378.0. In vivo, a growth inhibitory effect was observed with HDAC-I treatment, which was paralleled by a down-regulation of PCNA and a concomitant induction of apoptosis. Treatment of wild-type or knock-out HCT116 cells with A-423378.0 exerts potent anti-proliferative and pro-apoptotic effects in vitro and in vivo. A-423378.0 was able to induce apoptosis in both p21WAF1 and p53 deficient tumor cells, which appeared to be mediated by the intrinsic cell death pathway. Interestingly, the effects of A-423378.0 on the extrinsic cell death pathway through activation of TRAIL and its signaling pathway indicate that A-423378.0 may be a potent new therapeutic compound for the treatment of advanced colorectal cancer.

IT 179241-78-2
RL: BSU (Biological study, unclassified); BIOL (Biological study) (A-423378.0, histone deacetylase inhibitor, Bax- and TRAIL-related apoptosis inducing effect in colorectal cancer influenced by p53 or p21WAF1)

IT 9076-57-7
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor; A-423378.0, histone deacetylase inhibitor, cytotoxic effect in colorectal cancer influenced by p53 or p21WAF1)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 6 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 03 Dec 2007
ACCESSION NUMBER: 2007:1371984 HCAPLUS Full-text
DOCUMENT NUMBER: 148:236994
TITLE: Increased hepatotoxicity of tumor necrosis factor-related apoptosis-inducing ligand in diseased human liver
AUTHOR(S): Volkmann, Xandra; Fischer, Ute; Bahr, Matthias J.; Ott, Michael; Lehner, Frank; MacFarlane, Marion; Cohen, Gerald M.; Manns, Michael P.;

Schulze-Osthoff, Klaus; Bantel, Heike
CORPORATE SOURCE: Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany
SOURCE: Hepatology (Hoboken, NJ, United States) (2007), 46(5), 1498-1508
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis in tumor cells but not in most normal cells and has therefore been proposed as a promising antitumor agent. Recent expts. suggested that isolated primary human hepatocytes but not monkey liver cells are susceptible to certain TRAIL agonists, raising concerns about the use of TRAIL in cancer treatment. Whether TRAIL indeed exerts hepatotoxicity in vivo and how this is influenced by chemotherapeutic drugs or liver disease are completely unknown. Employing different forms of recombinant TRAIL, we found that the cytokine can induce proapoptotic caspase activity in isolated human hepatocytes. However in marked contrast, these different TRAIL prepns. induced little or no cytotoxicity when incubated with tissue explants of fresh healthy liver, an exptl. model that may more faithfully mimic the in vivo situation. In healthy liver, TRAIL induced apoptosis only when combined with histone deacetylase inhibitors. Strikingly, however, TRAIL alone triggered massive apoptosis accompanied by caspase activation in tissue explants from patients with liver steatosis or hepatitis C viral infection. This enhanced sensitivity of diseased liver was associated with an increased expression of TRAIL receptors and up-regulation of proapoptotic Bcl-2 proteins. Conclusion: These results suggest that clin. trials should be performed with great caution when TRAIL is combined with chemotherapy or administered to patients with inflammatory liver diseases.

L58 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 17 Jul 2007
ACCESSION NUMBER: 2007:771678 HCAPLUS Full-text
DOCUMENT NUMBER: 147:356465
TITLE: HDAC inhibitors induce apoptosis in glucocorticoid-resistant acute lymphatic leukemia cells despite a switch from the extrinsic to the intrinsic death pathway
AUTHOR(S): Tsapis, Michael; Lieb, Michele; Manzo, Fabio; Shankaranarayanan, Pattabhiraman; Herbrecht, Raoul; Lutz, Patrick; Gronemeyer, Hinrich
CORPORATE SOURCE: Department of Cell Biology and Signal Transduction, Institut de Genetique et de Biologie Moleculaire et Cellulaire (IGBMC)/CNRS/INSERM/ULP, C.U. de Strasbourg, F-67404, Fr.
SOURCE: International Journal of Biochemistry & Cell Biology (2007), 39(7-8), 1500-1509
CODEN: IJBBFU; ISSN: 1357-2725
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inhibitors of histone deacetylases (HDACi's) are promising novel tools for cancer therapy. We have compared the growth inhibitory and apoptogenic potential of the pan-HDACi SAHA and the sub-class I selective HDAC inhibitor MS275, as well as valproic acid (VPA) on glucocorticoid sensitive and resistant B (B-ALL) and T (T-ALL) cell acute lymphoblastic leukemia cells and patients blasts. In contrast, to our previous results with U937 acute myeloid

leukemia (AML) cells which showed a similar activity of MS275 and SAHA in growth inhibition and apoptosis induction, both B and T-ALL cells were much more efficiently killed by SAHA and VPA than by MS275. The same relative potency was observed with some patient ALL blasts treated ex vivo. SAHA displayed similar efficacy on glucocorticoid-sensitive and insensitive ALL cells but did not synergize with dexamethasone. In studying mediators of apoptosis we found that the TRAIL receptor DR5 is constitutively expressed in glucocorticoid-sensitive CEM-C7 cells which are also TRAIL sensitive. In contrast, glucocorticoid-insensitive CEM-C1 cells do not express DR5 and are insensitive to TRAIL. However, SAHA induces, in addition to p21WAF1/CIP1 also re-expression of DR5. Importantly, SAHA-induced apoptosis of CEM-C7 cells operates through initiator caspase 10, while it induces apoptosis of CEM-C1 cells through the intrinsic, as well as through caspase-independent death pathways. Our data suggest that the generation of resistance to glucocorticoids has dramatically altered death signaling in these cells and that SAHA overcomes these restrictions by inducing alternative death pathways.

IT 179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HDAC inhibitors induce apoptosis in glucocorticoid-resistant acute lymphatic leukemia cells)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; HDAC inhibitors induce apoptosis in glucocorticoid-resistant acute lymphatic leukemia cells)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 8 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 19 Jun 2007
ACCESSION NUMBER: 2007:658845 HCAPLUS Full-text
DOCUMENT NUMBER: 147:297746
TITLE: Membrane expression of DR4, DR5 and caspase-8 levels, but not Mcl-1, determine sensitivity of human myeloma cells to Apo2L/TRAIL
AUTHOR(S): Gomez-Benito, Maria; Martinez-Lorenzo, Maria Jose; Anel, Alberto; Marzo, Isabel; Naval, Javier
CORPORATE SOURCE: Departamento de Bioquimica y Biologia Molecular y Celular, Facultad de Ciencias, Universidad de Zaragoza, Zaragoza, 50009, Spain
SOURCE: Experimental Cell Research (2007), 313(11), 2378-2388
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The improved recombinant form of the death ligand Apo2L/ TRAIL (Apo2L/TRAIL.0) is not cytotoxic for normal human cells and is a good candidate for the therapy of multiple myeloma (MM), a B-cell neoplasia that remains incurable. The authors analyzed the mol. determinants of myeloma sensitivity to Apo2L/TRAIL.0 in a number of MM cell lines, the mechanisms of resistance, and a possible way of overcoming it. Expression of one death receptor for Apo2L/TRAIL (DR4 or DR5)
is sufficient to transduce death signals, though DR5 was more efficient when both receptors were present. Membrane expression of decoy receptors (DcR1, DcR2) and intracellular levels of c-FLIPL, XIAP, and Mcl-1 were not predictive of resistance to Apo2L/TRAIL. Inhibition of Mcl-1 degradation did not prevent Apo2L/TRAIL-induced apoptosis. In IM-9 cells, resistance was associated to a reduced caspase-8 expression. U266 cells, though expressing significant levels of DR4 and caspase-8, were nevertheless resistant to Apo2L/TRAIL. This

resistance could be overcome by co-treatment with valproic acid (VPA), a histone deacetylase inhibitor. VPA caused the redistribution of DR4 to plasma membrane lipid rafts and restored DR4 signaling. Overexpression of Mcl-1 in U266 cells did not prevent Apo2L/TRAIL cytotoxicity in VPA-sensitized cells. These results support the possible use of Apo2L/ TRAIL.0 in the treatment of MM.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 9 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 28 Feb 2007
ACCESSION NUMBER: 2007:216507 HCAPLUS Full-text
DOCUMENT NUMBER: 147:45438
TITLE: Histone deacetylase inhibitors enhance Ad5-TRAIL killing of TRAIL-resistant prostate tumor cells through increased caspase-2 activity
AUTHOR(S): VanOosten, Rebecca L.; Earel, James K., Jr.; Griffith, Thomas S.
CORPORATE SOURCE: Department of Urology, University of Iowa, Iowa City, IA, 52242-1089, USA
SOURCE: Apoptosis (2007), 12(3), 561-571
CODEN: APOPFN; ISSN: 1360-8185
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interest in TNF-related apoptosis-inducing ligand (TRAIL) as a cancer therapeutic has been high since its first description. Recently, the use of histone deacetylase inhibitors (HDACi) to treat cancer has progressed from the laboratory to the clinic, and the combination of HDACi and TRAIL is very powerful in killing human tumors. Using a panel of prostate tumor cell lines (ALVA-31, DU-145, and LNCaP) with varying TRAIL sensitivity, we examined their sensitization to a recombinant adenovirus encoding TRAIL (Ad5-TRAIL) by sodium butyrate and trichostatin A. HDACi treatment increased coxsackie-adenovirus receptor (CAR) expression, resulting in increased adenoviral infection, and increased TRAIL-mediated killing. In TRAIL-resistant DU-145 cells, HDAC inhibition also decreased protein kinase casein kinase (PKCK) 2 activity, leading to caspase-2 activation. The importance of PKCK2 and caspase-2 in DU-145 sensitization was demonstrated with the PKCK-2-specific inhibitor, which enhanced Ad5- TRAIL-induced death, or the caspase-2-specific inhibitor, zVDVAD, which blocked Ad5-TRAIL-induced death. Thus, our data highlight the connection between HDAC inhibition of PKCK2 activity and tumor cell sensitivity to TRAIL-induced apoptosis. Specifically, HDAC inhibition leads to decreased PCKC2 activity, which is followed by caspase-2 activation and partial cleavage of caspase-8 that sensitizes the tumor cell to TRAIL .

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 10 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 14 Feb 2007
ACCESSION NUMBER: 2007:164830 HCAPLUS Full-text
DOCUMENT NUMBER: 146:414428
TITLE: The histone deacetylase inhibitors depsipeptide and MS-275, enhance TRAIL gene therapy of LNCaP prostate cancer cells without adverse effects in normal prostate epithelial cells
AUTHOR(S): Kasman, L.; Lu, P.; Voelkel-Johnson, C.
CORPORATE SOURCE: Department of Microbiology & Immunology, Medical University of South Carolina, Charleston, SC, USA

SOURCE: Cancer Gene Therapy (2007), 14(3), 327-334
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gene therapy of cancer using adenovirus as a single treatment modality has met limited success and efforts to enhance therapeutic outcomes have included combination of gene therapy with chemotherapy. The goal of this study was to investigate which chemotherapeutic agents may be suitable for combination with gene therapy of prostate cancer. Using an adenovirus expressing green fluorescent protein (GFP), we determined the effect of cisplatin, gemcitabine, doxorubicin, depsipeptide and MS-275 on adenoviral infectivity and transgene expression in LNCaP cells. We found that the two histone deacetylase inhibitors (HDACi), depsipeptide and MS-275, and to a lesser extent doxorubicin, increased infectivity and transgene expression. However, only the HDACi selectively increased infectivity in LNCaP cells while doxorubicin increased infectivity to a greater extent in normal prostate epithelial cells (PrEC). The increase in infectivity but not transgene expression correlated to increased surface expression of coxsackie and adenovirus receptor (CAR). Increased transgene expression following infection with an adenovirus expressing tumor necrosis factor-related apoptosis inducing ligand (TRAIL) was observed only in LNCaP cells treated with depsipeptide or MS-275. Combination of TRAIL gene therapy with HDACi but not doxorubicin resulted in increased induction of apoptosis in LNCaP cells. In contrast, apoptosis was not enhanced by HDACi in normal PrEC. These results suggest that combination of HDACi with adenoviral TRAIL gene therapy may be a new therapeutic approach for the treatment of prostate cancer that warrants further investigation.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 11 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 22 Jan 2007
ACCESSION NUMBER: 2007:68913 HCAPLUS Full-text
DOCUMENT NUMBER: 146:114515
TITLE: Trichostatin A induces apoptosis in lung cancer cells via simultaneous activation of the death receptor-mediated and mitochondrial pathway
AUTHOR(S): Kim, Hak-Ryul; Kim, Eun-Jung; Yang, Sei-Hoon; Jeong, Eun-Taik; Park, Channy; Lee, Jae-Hyung; Youn, Myung-Ja; So, Hong-Seob; Park, Raekil
CORPORATE SOURCE: Department of Internal Medicine, Wonkwang University School of Medicine, Jeonbuk, 570-749, S. Korea
SOURCE: Experimental and Molecular Medicine (2006), 38(6), 616-624
CODEN: EMMEF3; ISSN: 1226-3613
PUBLISHER: Korean Society of Medical Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Trichostatin A (TSA), originally developed as an antifungal agent, is one of potent histone deacetylase (HDAC) inhibitors, which are known to cause growth arrest and apoptosis induction of transformed cells, including urinary bladder, breast, prostate, ovary, and colon cancers. However, the effect of HDAC inhibitors on human non-small cell lung cancer cells is not clearly known yet. Herein, we demonstrated that treatment of TSA resulted in a significant decrease of the viability of H157 cells in a dose-dependent manner, which was revealed as apoptosis accompanying with nuclear fragmentation and an increase in sub-G0/G1 fraction. In addition, it induced the expression of Fas/FasL,

which further triggered the activation of caspase-8. Catalytic activation of caspase-9 and decreased expression of anti-apoptotic Bcl-2 and Bcl-XL proteins were observed in TSA-treated cells. Catalytic activation of caspase-3 by TSA was further confirmed by cleavage of pro-caspase-3 and intracellular substrates, including poly (ADP-ribose) polymerase (PARP) and inhibitor of caspase-activated DNase (ICAD). In addition, a characteristic phenomenon of mitochondrial dysfunction, including mitochondrial membrane potential transition and release of mitochondrial cytochrome c into the cytosol was apparent in TSA-treated cells. Taken together, our data indicate that inhibition of HDAC by TSA induces the apoptosis of H157 cells through signaling cascade of Fas/FasL-mediated extrinsic and mitochondria-mediated intrinsic caspases pathway.

IT 179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(trichostatin A induces apoptosis in lung cancer cells via simultaneous activation of death receptor-mediated and mitochondrial pathway)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 12 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 19 Dec 2006
ACCESSION NUMBER: 2006:1326842 HCAPLUS Full-text
DOCUMENT NUMBER: 146:372040
TITLE: Rapid and profound potentiation of Apo2L/TRAIL-mediated cytotoxicity and apoptosis in thoracic cancer cells by the histone deacetylase inhibitor Trichostatin A: the essential role of the mitochondria-mediated caspase activation cascade
AUTHOR(S): Reddy, Rishindra M.; Yeow, Wen-Shuz; Chua, Alex; Nguyen, Duc M.; Baras, Aris; Ziauddin, M. Firdos; Shamimi-Noori, Susan M.; Maxhimer, Justin B.; Schrump, David S.; Nguyen, Dao M.
CORPORATE SOURCE: Section of Thoracic Oncology, Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Apoptosis (2007), 12(1), 55-71
CODEN: APOPFN; ISSN: 1360-8185
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Apo2L/TRAIL is actively investigated as a novel targeted agent to directly induce apoptosis of susceptible cancer cells. Apo2L/TRAIL-refractory cells can be sensitized to the cytotoxic effect of this ligand by cytotoxic chemotherapeutics. The aim of this study was to evaluate the in vitro tumoricidal activity of the Apo2L/TRAIL + Trichostatin A in cultured thoracic cancer cells and to elucidate the mol. basis of the synergistic cytotoxicity of this combination. Concurrent exposure of cultured cancer cells to sublethal concns. of Apo2L/TRAIL and Trichostatin A resulted in profound enhancement of Apo2L/TRAIL-mediated cytotoxicity in all cell lines regardless of their intrinsic susceptibility to this ligand. This combination was not toxic to primary normal cells. While Apo2L/TRAIL alone or Trichostatin A alone mediated <20% cell death, 60 to 90% of cancer cells were apoptotic following treatment with TSA + Apo2L/TRAIL combinations. Complete translocation of Bax from the cytosol to the mitochondria compartment was mainly observed in combination-treated cells and this was correlated with robust elevation of caspase 9 proteolytic activity indicative of activation of the mitochondria

apoptogenic effect. Profound TSA + Apo2L/TRAIL-mediated cytotoxicity and apoptosis were completely abrogated by either Bcl2 over-expression or by the selective caspase 9 inhibitor, highlighting the essential role of mitochondria-dependent apoptosis signaling cascade in this process. Moreover, increased caspase 8 activity observed in cells treated with the TSA + Apo2L/TRAIL combination was completely suppressed by Bcl-2 over-expression or by the selective caspase 9 inhibitor indicating that the elevated caspase 8 activity in combination-treated cells was secondary to a mitochondria-mediated amplification feedback loop of caspase activation. These finding form the basis for further development of HDAC inhibitors + Apo2L/TRAIL combination as novel targeted therapy for thoracic malignancies.

IT 9076-57-7, Histone deacetylase
179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cytotoxic effects of Apo2L/TRAIL combined with Trichostatin A in thoracic cancer cells via mitochondria-mediated caspase activation cascade)

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 13 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 18 Dec 2006
ACCESSION NUMBER: 2006:1320798 HCAPLUS Full-text
DOCUMENT NUMBER: 146:242993
TITLE: Histone deacetylase inhibitors as a treatment of TRAIL-resistant cancers
AUTHOR(S): Neuzil, Jiri; Andera, Ladislav; Gabrielli, Brian
CORPORATE SOURCE: Apoptosis Research Group, School of Health Science, Griffith University, Southport, QLD, Australia
SOURCE: Application of Apoptosis to Cancer Treatment (2005), 271-291. Editor(s): Sluyser, Mels. Springer: Dordrecht, Neth. CODEN: 69ISEX; ISBN: 978-1-4020-3303-2
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review. Histone deacetylase inhibitors (HDIs) are a novel prospective group of potential anti-cancer agents, some of them being tested in a clin. setting. The major mode of action of these compds. is inhibition of the cell cycle transition and, consequently, differential regulation of a number of genes necessary for cell proliferation, while favoring expression of genes rather associated with anti-proliferative pathways and with cell death signalling. This implies a possible role of HDIs in adjuvant treatment of tumors resistant to other agents, operating via a different mol. mechanism. The TNF-related apoptosis-inducing ligant (TRAIL) is a promising immunol. inducer of apoptosis efficient against a variety of tumors with a remarkably selective mode of action. However, some malignancies are resistant to TRAIL treatment. In this paper, we review our current knowledge on HDI-mediated sensitization of TRAIL-non-responsive tumors to this apoptogen and suggest a future clin. potential of HDIs and TRAIL in cancer management.

REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 14 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 13 Oct 2006
ACCESSION NUMBER: 2006:1066885 HCAPLUS Full-text
DOCUMENT NUMBER: 145:410637
TITLE: Honokiol derivatives for the treatment of proliferative disorders

INVENTOR(S): Arbiser, Jack L.; Amblard, Frank
PATENT ASSIGNEE(S): Emory University, USA
SOURCE: PCT Int. Appl., 233pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006107451	A2	20061012	WO 2006-US6494	20060223
WO 2006107451	A3	20061130		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2006233101	A1	20061012	AU 2006-233101	20060223
CA 2600065	A1	20061012	CA 2006-2600065	20060223
EP 1853539	A2	20071114	EP 2006-735955	20060223
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN 101223120	A	20080716	CN 2006-80013726	20071023

PRIORITY APPLN. INFO.:	US 2005-655346P	P	20050223
	WO 2006-US6494	W	20060223

OTHER SOURCE(S): MARPAT 145:410637

AB The invention provides honokiol derivs., as well as pharmaceutical compns. containing the honokiol derivs. These compds. and pharmaceutical compns. can be used in the prevention and/or treatment of cancer. In particular, honokiol derivs., pharmaceutical compns. comprising the derivs., and methods for their use in the treatment of myeloma are provided. Compound preparation is described.

IT 179241-78-2, Caspase 8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(honokiol derivs. for treatment of proliferative disorders)

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, combination; honokiol derivs. for treatment of proliferative disorders)

L58 ANSWER 15 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 28 Sep 2006
ACCESSION NUMBER: 2006:1006362 HCAPLUS Full-text
DOCUMENT NUMBER: 145:369905
TITLE: Treatment of protein degradation disorders
INVENTOR(S): Anderson, Kenneth C.; Bradner, James Elliott; Greenberg, Edward Franklin; Hideshima, Teru; Kwiatkowski, Nicholas Paul; Mazitschek, Ralph; Schreiber, Stuart L.; Shaw, Jared
PATENT ASSIGNEE(S): The President and Fellows of Harvard College, USA;

Dana-Farber Cancer Institute, Inc.
SOURCE: PCT Int. Appl., 194pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006102557	A2	20060928	WO 2006-US10676	20060322
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2006226861	A1	20060928	AU 2006-226861	20060322
CA 2601706	A1	20060928	CA 2006-2601706	20060322
US 20060239909	A1	20061026	US 2006-386959	20060322
EP 1861126	A2	20071205	EP 2006-748614	20060322
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
IN 2007KN04029	A	20080328	IN 2007-KN4029	20071018

PRIORITY APPLN. INFO.: US 2005-664470P P 20050322
WO 2006-US10676 W 20060322

OTHER SOURCE(S): MARPAT 145:369905

AB The invention relates to methods of treating protein degradation disorders, such cellular proliferative disorders (e.g., cancer) and protein deposition disorders (e.g., neurodegenerative disorders). The invention provides methods and pharmaceutical compns. for treating these diseases using aggresome inhibitors or combinations of aggresome inhibitors and proteasome inhibitors. The invention further relates to methods and pharmaceutical compns. for treating multiple myeloma. New HDAC (histone deacetylase)/TDAC (tubulin deacetylase) inhibitors and aggresome inhibitors are also provided as well as synthetic methodologies for preparing these compds.

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (6, inhibitors and peptides derived from; treatment of protein degradation disorders using protein degradation inhibitors in relation to cellular phenotype determination and screening and combination with other agents)

IT 438496-81-2, Tubulin deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; treatment of protein degradation disorders using protein degradation inhibitors in relation to cellular phenotype determination and screening and combination with other agents)

IT 179241-78-2, Caspase 8
RL: BSU (Biological study, unclassified); BIOL (Biological study) (of plasma cells, phenotype; treatment of protein degradation disorders using protein degradation inhibitors in relation to cellular phenotype

determination and screening and combination with other agents)

IT 404950-80-7, LBH 589
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of protein degradation disorders using protein degradation inhibitors in relation to cellular phenotype determination and screening and combination with other agents)

L58 ANSWER 16 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 25 Sep 2006
ACCESSION NUMBER: 2006:990247 HCAPLUS Full-text
DOCUMENT NUMBER: 147:935
TITLE: Antitumor activity of suberoylanilide hydroxamic acid against thyroid cancer cell lines in vitro and in vivo
AUTHOR(S): Luong, Quang T.; O'Kelly, James; Braunstein, Glenn D.; Hershman, Jerome M.; Koeffler, H. Phillip
CORPORATE SOURCE: Department of Medicine and the Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center, University of California at Los Angeles School of Medicine, Los Angeles, CA, USA
SOURCE: Clinical Cancer Research (2006), 12(18), 5570-5577
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), has multiple antitumor effects against a variety of human cancers. We treated several anaplastic and papillary thyroid cancer cell lines with SAHA to determine if it could inhibit the growth of these cells in vitro and in vivo. SAHA effectively inhibited 50% clonal growth of the anaplastic thyroid cancer cell lines, ARO and FRO, and the papillary thyroid cancer cell line, BHP 7-13, at 1.3 + 10-7 to 5 + 10-7 mol/L, doses that are achievable in patients. In concert with growth inhibition, SAHA down-regulated the expression of cyclin D1 and up-regulated levels of p21WAF1. Annexin V and cleavage of poly(ADP)ribose polymerase were both increased by exposure of the thyroid cancer cells to SAHA. Expression of the death receptor 5 (DR5) gene was also increased by SAHA, but the combination of the DR5 ligand, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), with SAHA had little effect compared with SAHA alone. Of note, the combination of paclitaxel, doxorubicin, or paraplatin with SAHA enhanced cell killing of the thyroid cancer cells. In addition, murine studies showed that SAHA administered daily by i.p. injection at 100 mg/kg inhibited the growth of human thyroid tumor cells. The data indicate that SAHA is a plausible adjuvant therapy for thyroid cancers.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 17 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 25 Jul 2006
ACCESSION NUMBER: 2006:719603 HCAPLUS Full-text
DOCUMENT NUMBER: 146:38659
TITLE: Trichostatin A sensitizes rheumatoid arthritis synovial fibroblasts for TRAIL-induced apoptosis
AUTHOR(S): Jungel, A.; Baresova, V.; Ospelt, C.; Simmen, B. R.; Michel, B. A.; Gay, R. E.; Gay, S.; Seemayer, C. A.; Neidhart, M.
CORPORATE SOURCE: Centre of Experimental Rheumatology, University Hospital Zurich, Zurich, CH 8091, Switz.

SOURCE: Annals of the Rheumatic Diseases (2006), 65(7), 910-912
CODEN: ARDIAO; ISSN: 0003-4967
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Histone acetylation/deacetylation has a critical role in the regulation of transcription by altering the chromatin structure. To analyze the effect of trichostatin A (TSA), a streptomyces metabolite which specifically inhibits mammalian histone deacetylases, on TRAIL-induced apoptosis of rheumatoid arthritis synovial fibroblasts (RASF). Apoptotic cells were detected after co-treatment of RASF with TRAIL (200 ng/mL) and TSA (0.5, 1, and 2 μmol/l) by flow cytometry using propidium iodide/annexin-V-FITC staining. Cell proliferation was assessed using the MTS proliferation test. Induction of the cell cycle inhibitor p21Waf/Cip1 by TSA was analyzed by western blot. Expression of the TRAIL receptor-2 (DR5) on the cell surface of RASF was analyzed by flow cytometry. Levels of soluble TRAIL were measured in synovial fluid of patients with RA and osteoarthritis (OA) by ELISA. Co-treatment of the cells with TSA and TRAIL induced cell death in a synergistic and dose dependent manner, whereas TRAIL and TSA alone had no effect or only a modest effect. RASF express DR5 (TRAIL receptor 2), but treatment of the cells with TSA for 24 h did not change the expression level of DR5, as it is shown for cancer cells. TSA induced cell cycle arrest in RASF through up regulation of p21Waf1/Cip1. Levels of soluble TRAIL were significantly higher in RA than in OA synovial fluids. Because TSA sensitizes RASF for TRAIL-induced apoptosis, it is concluded that TSA discloses sensitive sites in the cascade of TRAIL signalling and may represent a new principle for the treatment of RA.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 18 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 20 Jul 2006
ACCESSION NUMBER: 2006:703970 HCAPLUS Full-text
DOCUMENT NUMBER: 145:202241
TITLE: The histone deacetylase inhibitor, suberoylanilide hydroxamic acid, overcomes resistance of human breast cancer cells to Apo2L/TRAIL
AUTHOR(S): Butler, Lisa M.; Liapis, Vasilios; Bouralexis, Stelios; Welldon, Katie; Hay, Shelley; Thai, Le M.; Labrinidis, Agatha; Tilley, Wayne D.; Findlay, David M.; Evdokiou, Andreas
CORPORATE SOURCE: Dame Roma Mitchell Cancer Research Laboratories, University of Adelaide and Hanson Institute, Adelaide, SA, Australia
SOURCE: International Journal of Cancer (2006), 119(4), 944-954
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB While the apoptosis-inducing ligand Apo2L/TRAIL is a promising new agent for the treatment of cancer, the sensitivity of cancer cells for induction of apoptosis by Apo2L/TRAIL varies considerably. Identification of agents that can be used in combination with Apo2L/TRAIL to enhance apoptosis in breast cancer cells would increase the potential utility of this agent as a breast cancer therapeutic. Here, we show that the histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), can sensitize Apo2L/ TRAIL-resistant breast cancer cells to Apo2L/ TRAIL-induced appotosis. Importantly, neither Apo2L /TRAIL alone, nor in combination with SAHA, affected the viability of

normal human cells in culture. Apo2L /TRAIL-resistant MDA-MB-231 breast cancer cells, generated by long-term culture in the continuous presence of Apo2L/ TRAIL, were resensitized to Apo2L/TRAIL -induced apoptosis by SAHA. The sensitization of these cells by SAHA was accompanied by activation of caspase 8, caspase 9 and caspase 3 and was concomitant with Bid and PARP cleavage. The expression of the proapoptotic protein, Bax, increased significantly with SAHA treatment and high levels of Bax were maintained in the combined treatment with Apo2L/TRAIL. Treatment with SAHA increased cell surface expression of DR5 but not DR4. Interestingly, SAHA treatment also resulted in a significant increase in cell surface expression of DcR1. Taken together, our findings indicate that the use of these 2 agents in combination may be effective for the treatment of breast cancer.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 19 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 26 May 2006
ACCESSION NUMBER: 2006:495287 HCAPLUS Full-text
DOCUMENT NUMBER: 145:499424
TITLE: HDAC inhibitors: Double edge sword for TRAIL cancer therapy?
AUTHOR(S): Fulda, Simone; Debatin, Klaus-Michael
CORPORATE SOURCE: University Children's Hospital, Ulm, Germany
SOURCE: Cancer Biology & Therapy (2005), 4(10), 1113-1115
CODEN: CBTAAO; ISSN: 1538-4047
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The research of VanOosten et al. (2005) entitled " Histone deacetylase inhibitors modulate renal cell carcinoma sensitivity to TRAIL/Apo-2L -induced apoptosis by enhancing TRAIL-R2 expression" is reviewed with commentary and refs. This study found that pretreatment with subtoxic concns. of histone deacetylase inhibitors (HDACI) sensitized resistant 786-0 human renal cell carcinoma cells towards TNF-related apoptosis-inducing ligand (TRAIL). The study raises serious concerns about the cancer-selective action of HDACI when used in combination with TRAIL, which has broad implications for cancer therapy.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 20 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 18 May 2006
ACCESSION NUMBER: 2006:459135 HCAPLUS Full-text
DOCUMENT NUMBER: 145:6250
TITLE: Apo2l/Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Prevents Breast Cancer-Induced Bone Destruction in a Mouse Model
AUTHOR(S): Thai, Le Minh; Labrinidis, Agatha; Hay, Shelley; Liapis, Vasilios; Bouralexis, Steve; Welldon, Katie; Coventry, Brendon J.; Findlay, David M.; Evdokiou, Andreas
CORPORATE SOURCE: Department of Orthopaedics, Royal Adelaide Hospital, Adelaide, 5000, Australia
SOURCE: Cancer Research (2006), 66(10), 5363-5370
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Breast cancer is the most common carcinoma that metastasizes to bone. To examine the efficacy of recombinant soluble Apo2 ligand (Apo2L)/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) against breast cancer growth in bone, we established a mouse model in which MDA-MB-231 human breast cancer cells were transplanted directly into the marrow cavity of the tibiae of athymic nude mice producing osteolytic lesions in the area of injection. All vehicle-treated control animals developed large lesions that established in the marrow cavity, eroded the cortical bone, and invaded the surrounding soft tissue, as assessed by radiog., micro-computed tomog., and histol. In contrast, animals treated with recombinant soluble Apo2L/TRAIL showed significant conservation of the tibiae, with 85% reduction in osteolysis, 90% reduction in tumor burden, and no detectable soft tissue invasion. Tumor cells explanted from Apo2L/TRAIL-treated animals were significantly more resistant to the effects of Apo2L/ TRAIL when compared with the cells explanted from the vehicle- treated control animals, suggesting that prolonged treatment with Apo2/TRAIL in vivo selects for a resistant phenotype. However, such resistance was readily reversed when Apo2L/TRAIL was used in combination with clin. relevant chemotherapeutic drugs, including taxol, etoposide, doxorubicin, cisplatin, or the histone deacetylase inhibitor suberoylanilide hydroxamic acid. These studies show for the first time that Apo2L/TRAIL can prevent breast cancer-induced bone destruction and highlight the potential of this ligand for the treatment of metastatic breast cancer in bone.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 21 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 03 Apr 2006
ACCESSION NUMBER: 2006:306923 HCAPLUS Full-text
DOCUMENT NUMBER: 145:465230
TITLE: HDAC inhibitor treatment of hepatoma cells induces both TRAIL-independent apoptosis and restoration of sensitivity to TRAIL
AUTHOR(S): Pathil, Anita; Armeanu, Sorin; Venturelli, Sascha; Mascagni, Paolo; Weiss, Thomas S.; Gregor, Michael; Lauer, Ulrich M.; Bitzer, Michael
CORPORATE SOURCE: Department of Internal Medicine I, Medical University Clinic, Tuebingen, Germany
SOURCE: Hepatology (Hoboken, NJ, United States) (2006), 43(3), 425-434
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hepatocellular carcinoma (HCC) displays a striking resistance to chemotherapeutic drugs or innovative tumor cell apoptosis-inducing agents such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Recently, we found 2 histone deacetylase inhibitors (HDAC-I), valproic acid and ITF2357, exhibiting inherent therapeutic activity against HCC. In TRAIL-sensitive cancer cells, the mechanism of HDAC-I-induced cell death has been identified to be TRAIL-dependent by inducing apoptosis in an autocrine fashion. In contrast, in HCC-derived cells, a prototype of TRAIL-resistant tumor cells, we found a HDAC-I-mediated apoptosis that works independently of TRAIL and upregulation of death receptors or their cognate ligands. Interestingly, TRAIL resistance could be overcome by a combinatorial application of HDAC-I and TRAIL, increasing the fraction of apoptotic cells two- to threefold compared with HDAC-I treatment alone, whereas any premature HDAC-I withdrawal rapidly restored TRAIL resistance. Furthermore, a tumor cell-specific downregulation of the FLICE inhibitory protein (FLIP) was observed, constituting a new

mechanism of TRAIL sensitivity restoration by HDAC-I. In contrast, FLIP levels in primary human hepatocytes (PHH) from different donors were upregulated by HDAC-I. Importantly, combination HDAC-I/TRAIL treatment did not induce any cytotoxicity in nonmalignant PHH. In conclusion, HDAC-I compds., exhibiting a favorable in vivo profile and inherent activity against HCC cells, are able to selectively overcome the resistance of HCC cells toward TRAIL. Specific upregulation of intracellular FLIP protein levels in nonmalignant hepatocytes could enhance the therapeutic window for clin. applications of TRAIL, opening up a highly specific new treatment option for advanced HCC.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 22 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 17 Mar 2006
ACCESSION NUMBER: 2006:239838 HCAPLUS Full-text
DOCUMENT NUMBER: 145:201619
TITLE: Exploiting the TSA connections to overcome apoptosis-resistance
AUTHOR(S): Ranganathan, Padhma; Rangnekar, Vivek M.
CORPORATE SOURCE: Graduate Center for Toxicology, University of Kentucky, Lexington, KY, USA
SOURCE: Cancer Biology & Therapy (2005), 4(4), 391-392
CODEN: CBTAAO; ISSN: 1538-4047
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The research of Taghiyev et al. entitled "Trichostatin A (TSA) sensitizes the human prostatic cancer cell line DU145 to death receptor ligands treatment" is reviewed with commentary and refs. Taghiyev et al. show that treatment of prostatic cancer cell line DU145 with TSA overcomes the resistance to apoptosis encountered with death receptor ligand-treatment. They further reveal that tumor-necrosis factor-α and anti-Fas antibody induce apoptotic cell death when used in conjunction with TSA. They demonstrate that the apoptotic outcome is not restricted to a single type of histone deacetylase inhibitors (HDIs), by using two types of inhibitors, TSA and depsipeptide. They observed that while caspase activation of these ligands alone is about the same as that observed in combination with TSA, apoptosis under combined treatment far exceeds that induced TNF-α or anti-Fas antibody alone, suggesting synergistic mechanism of action.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 23 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 17 Mar 2006
ACCESSION NUMBER: 2006:239836 HCAPLUS Full-text
DOCUMENT NUMBER: 145:202128
TITLE: Trichostatin A (TSA) sensitizes the human prostatic cancer cell line DU145 to death receptor ligands treatment
AUTHOR(S): Taghiyev, Agshin F.; Guseva, Natalya V.; Sturm, Mary T.; Rokhlin, Oskar W.; Cohen, Michael B.
CORPORATE SOURCE: Departments of Pathology, The University of Iowa, Iowa City, IA, USA
SOURCE: Cancer Biology & Therapy (2005), 4(4), 382-390
CODEN: CBTAAO; ISSN: 1538-4047
PUBLISHER: Landes Bioscience
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The human prostatic carcinoma cell line DU145 has previously been found to be resistant to treatment with TNF-family ligands. However, TRAIL, TNF-α and anti-Fas antibodies (Ab) treatment in combination with the histone deacetylase inhibitor Trichostatin A (TSA) converted the phenotype of DU145 from resistant to sensitive. TSA induced 15% cell death but simultaneous treatment with TRAIL, TNF-α and anti-Fas Ab resulted in 55%, 70% and 40% cell death, resp. Simultaneous treatment did not increase the level of TSA-induced histone acetylation, but induced the release of acetylated histones from chromatin into the cytosol. This release was caspase dependent since it was abrogated by Z-VAD-fmk. In addition, treatment with TSA induced caspase-9 activation and resulted in the release of cytochrome c and Smac/DIABLO from mitochondria. To further investigate the role of caspase-9 in TSA-mediated apoptosis we used two different approaches: (1) cells were pretreated with the caspase-9 inhibitor Z-LEHD-fmk, and (2) cells were transfected with a dominant-neg. form of caspase-9. Both approaches gave similar results: cells became resistant to treatment with TSA. These data indicate that TSA mediates its effect via the mitochondrial pathway. This was confirmed by examining DU145 overexpressing Bcl-2. These transfectants were resistant to TSA treatment. Taken together, our data shows that only simultaneous treatment with TNF-family ligands and TSA in DU145 resulted in caspase activity sufficient to induce apoptosis. The combination of TSA and TNF-family ligands could potentially be the basis for the treatment of prostate cancer.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 24 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN

ED Entered STN: 06 Jan 2006

ACCESSION NUMBER: 2006:15168 HCAPLUS Full-text

DOCUMENT NUMBER: 144:184210

TITLE: Histone Deacetylase Inhibitors Modulate the Sensitivity of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand-Resistant Bladder Tumor Cells

AUTHOR(S): Earel, James K., Jr.; VanOosten, Rebecca L.; Griffith, Thomas S.

CORPORATE SOURCE: Department of Urology, University of Iowa, Iowa City, IA, USA

SOURCE: Cancer Research (2006), 66(1), 499-507
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Urothelial carcinoma of the bladder accounts for .apprx.5% of all cancer deaths in humans. The large majority of tumors are superficial at diagnosis and, after local surgical therapy, have a high rate of local recurrence and progression. Current treatments extend time to recurrence but do not alter disease survival. The objective of the present study was to investigate the tumoricidal potential of combining the apoptosis-inducing protein tumor necrosis factor-related apoptosis inducing ligand (TRAIL) with histone deacetylase inhibitors (HDACi) against TRAIL -resistant bladder tumor cells. Pretreatment with HDACi at nontoxic doses, followed by incubation with TRAIL, resulted in a marked increase in TRAIL-induced apoptosis of T24 cells but showed no significant increase in toxicity to SV40 immortalized normal human uroepithelial cell-1. HDAC inhibition, especially with sodium butyrate and trichostatin A, led to increased TRAIL-R2 gene transcription that correlated with increased TRAIL-R2 surface expression. The increased TRAIL-R2 levels also resulted in accelerated death-inducing signaling complex (DISC) formation, caspase activation, and loss of mitochondrial membrane potential,

which all contributed to the increase in tumor cell death. Collectively, these results show the therapeutic potential of combining HDAC inhibition with TRAIL as an alternative treatment for bladder cancer.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 19 Dec 2005
ACCESSION NUMBER: 2005:1318528 HCAPLUS Full-text
DOCUMENT NUMBER: 144:324317
TITLE: Interactive effects of histone deacetylase inhibitors and TRAIL on apoptosis in human leukemia cells: involvement of both death receptor and mitochondrial pathways
AUTHOR(S): Shankar, Sharmila; Singh, Thiyam R.; Fandy, Tamer E.; Luetrakul, Thitidaj; Ross, Douglas D.; Srivastava, Rakesh K.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Molecular and Cellular Biology Program, University of Maryland, Baltimore, MD, 21201-1180, USA
SOURCE: International Journal of Molecular Medicine (2005), 16(6), 1125-1138
CODEN: IJMMFG; ISSN: 1107-3756
PUBLISHER: International Journal of Molecular Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study, we aimed to elucidate the mechanism responsible for the interactive effects of histone deacetylase (HDAC) inhibitors [suberoylanilide hydroxamic acid (SAHA), MS-275, m-carboxycinnamic acid bishydroxamide (CBHA), and trichostatin-A (TSA)] and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) on apoptosis in leukemia cells. HDAC inhibitors enhance the apoptosis-inducing potential of TRAIL in leukemia cells (HL60, Jurkat, K562, and U937) through multiple mechanisms; up-regulation of DR4, DR5, Bak, Bax, Bim, Noxa and PUMA, down-regulation of IAPs, Mcl-1, Bcl-2, Bcl-XL and cFLIP, release of mitochondrial proteins (cytochrome c, Smac/DIABLO and Omi/Htr2) to the cytosol, induction of p21WAF1/CIP1 and p27KIP1, activation of caspase-3 and cleavage of poly(ADP-ribose) polymerase (PARP). The sequential treatment of cells with HDAC inhibitors followed by TRAIL was more effective in inducing apoptosis than the concurrent treatment or single agent alone. The up-regulation of death receptors and inhibition of cFLIP by HDAC inhibitors will increase the ability of TRAIL to induce apoptosis, due to enhance activation of caspase-8, cleavage of Bid, and release of mitochondrial proteins to the cytosol, and subsequent activation of caspase-9 and caspase-3. Thus, the combination of HDAC inhibitors and TRAIL can be used as a new therapeutic approach for the treatment of leukemia.

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (increased activation of caspase, cleavage of Bid and release of mitochondrial protein to cytosol, death receptor up-regulation and cFLIP inhibition by HDAC inhibitors increased ability of TRAIL to induce apoptosis in leukemia cell)

IT 179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study) (increased activation of caspase-8, cleavage of Bid and release of mitochondrial protein to cytosol and subsequent activation of caspase-9 and caspase-3 by HDAC inhibitors increased ability of TRAIL to induce apoptosis in leukemia cell)

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE

RE FORMAT

L58 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 23 Sep 2005
ACCESSION NUMBER: 2005:1028418 HCAPLUS Full-text
DOCUMENT NUMBER: 143:318614
TITLE: Sodium butyrate sensitizes human pancreatic cancer cells to both the intrinsic and the extrinsic apoptotic pathways
AUTHOR(S): Natoni, Federica; Diolordi, Laura; Santoni, Claudio; Gilardini Montani, Maria Saveria
CORPORATE SOURCE: Department of Environmental Science, University of La Tuscia, Viterbo, Italy
SOURCE: Biochimica et Biophysica Acta, Molecular Cell Research (2005), 1745(3), 318-329
CODEN: BBAMCO; ISSN: 0167-4889
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pancreatic cancer is characterized by a highly malignant phenotype with a marked resistance to conventional therapies and to apoptotic activators. Here, we demonstrate that sodium butyrate (NaBt), an inhibitor of histone deacetylases, sensitizes human pancreatic cancer cell lines to both mitochondria- and Fas-mediated apoptosis. The anal. of anti-apoptotic and pro-apoptotic members of the Bcl-2 family in untreated pancreatic cancer cell lines shows a generalized low expression of Bcl-2 and a strong expression of Bcl-xL. NaBt treatment results in a marked down-regulation of Bcl-xL expression, mitochondrial membrane depolarization, cytochrome c release from mitochondria, activation of caspase-9 and -3 and apoptosis induction. Furthermore, NaBt sensitizes pancreatic cancer cells to Fas-mediated apoptosis as well. In fact, the combined treatment with NaBt and the agonistic antibody anti-Fas (CH11) is able to induce apoptosis at an early time, in which neither NaBt nor CH11 alone induce apoptosis. Down-regulation of FLIP and activation of caspase-8 allow apoptosis to occur. These findings suggest that sodium butyrate could represent a good candidate for the development of new therapeutic strategies aimed at improving chemotherapy and immunotherapy in pancreatic cancer.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 27 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 04 Aug 2005
ACCESSION NUMBER: 2005:693615 HCAPLUS Full-text
DOCUMENT NUMBER: 143:451828
TITLE: Histone deacetylase inhibitors: insights into mechanisms of lethality
AUTHOR(S): Rosato, Roberto R.; Grant, Steven
CORPORATE SOURCE: Medical College of Virginia, Department of Medicine, Virginia Commonwealth University, Richmond, VA, 23298, USA
SOURCE: Expert Opinion on Therapeutic Targets (2005), 9(4), 809-824
CODEN: EOTTAO; ISSN: 1472-8222
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Histone deacetylases (HDACs) have recently emerged as an important target for therapeutic intervention in cancer and potentially other human diseases. By modulating the acetylation status of histones, histone

deacetylase inhibitors (HDACIs) alter the transcription of genes involved in cell growth, maturation, survival and apoptosis, among other processes. Early clin. results suggest a potentially useful role for HDACIs in the treatment of certain forms of lymphoma (e.g., cutaneous T cell lymphoma) and acute leukemia. An unresolved question is how HDACIs induce cell death in tumor cells. Recent studies suggest that acetylation of nonhistone proteins may play an important role in the biol. effects of this class of compds., and may explain lack of correlation between histone acetylation and induction of cell death by HDACIs in some circumstances. Recently, attention has focussed on the effects of HDACIs on disruption of co-repressor complexes, induction of oxidative injury, upregulation of the expression of death receptors, generation of lipid second messengers such as ceramide, interference with the function of chaperone proteins and modulation of the activity of NF-κB as critical determinants of lethality. Aside from providing critical insights into the mechanism of action of HDACIs in neoplastic disease, these findings may provide a foundation for the rational development of combination studies, involving HDACIs in combination with either conventional cytotoxic drugs as well as more novel targeted agents.

REFERENCE COUNT: 194 THERE ARE 194 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 28 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 07 Jul 2005
ACCESSION NUMBER: 2005:585236 HCAPLUS Full-text
DOCUMENT NUMBER: 143:186322
TITLE: HDAC inhibitors enhance the apoptosis-inducing potential of TRAIL in breast carcinoma
AUTHOR(S): Singh, Thiyam Ramsing; Shankar, Sharmila; Srivastava, Rakesh K.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Molecular and Cellular Biology Program, Greenebaum Cancer Center, University of Maryland, Baltimore, MD, 21201-1180, USA
SOURCE: Oncogene (2005), 24(29), 4609-4623
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Histone deacetylase (HDAC) inhibitors induce differentiation and/or apoptosis in a variety of cell types by activating transcription of target genes. Activation of the death receptor (DR) pathway by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis preferentially in cancer cells. Here, we investigated the intracellular mechanisms by which HDAC inhibitors (suberoylanilide hydroxamic acid, m-carboxycinnamic acid bis-hydroxamide, MS-275 and trichostatin A) enhance the apoptosis-inducing potential of TRAIL in breast cancer cells in vitro. A synergism in apoptosis was observed in both TRAIL-sensitive and -resistant cells upon sequential treatments with HDAC inhibitors followed by TRAIL. HDAC inhibitors synergized with TRAIL by inducing DRs DR4/TRAIL-R1 and DR5/TRAIL -R2 through NFκB activation and some of the proapoptotic members of the Bcl-2 family, and engaging the mitochondrial pathway. The ability of HDAC inhibitors to sensitize TRAIL -resistant cells suggests that HDAC inhibitors may induce fundamental alterations in cell signaling pathways. Thus, the sequential treatments with HDAC inhibitors followed by TRAIL may be used as a new therapeutic approach for the treatment of human cancers.

REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 29 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 16 Jun 2005
ACCESSION NUMBER: 2005:516036 HCAPLUS Full-text
DOCUMENT NUMBER: 143:458226
TITLE: Chronic lymphocytic leukemic cells exhibit apoptotic signaling via TRAIL-R1
AUTHOR(S): MacFarlane, M.; Inoue, S.; Kohlhaas, S. L.; Majid, A.; Harper, N.; Kennedy, D. B. J.; Dyer, M. J. S.; Cohen, G. M.
CORPORATE SOURCE: MRC Toxicology Unit, Hodgkin Building, University of Leicester, Leicester, LE1 9HN, UK
SOURCE: Cell Death and Differentiation (2005), 12(7), 773-782
CODEN: CDDIEK; ISSN: 1350-9047
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Clin. trials have been initiated with Apo2L/TRAIL (Genentech) and agonistic mAbs to TRAIL receptors, -R1 and -R2 (Human Genome Sciences). The apoptosis-inducing ability of these mAbs and different TRAIL prepns., in the presence or absence of histone deacetylase inhibitors (HDACi), varied markedly against primary chronic lymphocytic leukemia (CLL) cells and various tumor cell lines, demonstrating an unanticipated preferential apoptotic signaling via either TRAIL-R1 or -R2. Contrary to literature reports that TRAIL-induced apoptosis occurs primarily via signaling through TRAIL-R2, CLL cells, in the presence of HDACi, undergo predominantly TRAIL-R1-mediated apoptosis. Consequently, Apo2L/TRAIL, which signals primarily through TRAIL-R2, is virtually devoid of activity against CLL cells. To maximize therapeutic benefit, it is essential to ascertain whether a primary tumor signals via TRAIL -R1/-R2, prior to initiating therapy. Thus combination of an agonistic TRAIL-R1 Ab and an HDACi, such as the anticonvulsant sodium valproate, could be of value in treating CLL.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 30 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 25 Mar 2005
ACCESSION NUMBER: 2005:259910 HCAPLUS Full-text
DOCUMENT NUMBER: 142:329825
TITLE: Combination of a histone deacetylase inhibitor with a death receptor ligand
INVENTOR(S): Atadja, Peter Wisdom; Bhalla, Kapil N.
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH; University of South Florida Board of Trustees
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005025619	A1	20050324	WO 2004-EP10468	20040917
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,				

MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ,
DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL,
PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

AU 2004271730	A1	20050324	AU 2004-271730	20040917
CA 2539000	A1	20050324	CA 2004-2539000	20040917
EP 1667720	A1	20060614	EP 2004-765360	20040917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1852737	A	20061025	CN 2004-80026541	20040917
BR 2004014506	A	20061107	BR 2004-14506	20040917
JP 2007505860	T	20070315	JP 2006-526597	20040917
IN 2006CN00926	A	20070615	IN 2006-CN926	20060316
MX 2006PA03127	A	20061017	MX 2006-PA3127	20060317
US 20070258972	A1	20071108	US 2007-571734	20070319
PRIORITY APPLN. INFO.:			US 2003-504655P P	20030918
			WO 2004-EP10468 W	20040917

OTHER SOURCE(S): MARPAT 142:329825

AB The invention relates to a method of preventing or treating proliferative diseases such as cancer in a mammal, particularly a human, with a combination of pharmaceutical agents which comprises: (a) a histone deacetylase inhibitor (HDAI); and (b) a death receptor ligand. The invention further relates to pharmaceutical compns. comprising: (a) an HDAI; (b) death receptor ligand; and (c) a pharmaceutically acceptable carrier. The present invention further relates to a com. package or product comprising: (a) a pharmaceutical formulation of an HDAI; and (b) a pharmaceutical formulation of death receptor ligand for simultaneous, concurrent, sep. or sequential use.

IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination of a histone deacetylase inhibitor
with a death receptor ligand for treating proliferative diseases
such as cancer in relation to effect on death inducing signaling)

IT 404950-80-7 404951-52-6 404951-53-7
RL: PAC (Pharmacological activity); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(combination of a histone deacetylase inhibitor
with a death receptor ligand for treating proliferative diseases
such as cancer in relation to effect on death inducing signaling)

IT 179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induction; combination of a histone deacetylase
inhibitor with a death receptor ligand for treating proliferative
diseases such as cancer in relation to effect on death inducing
signaling)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 31 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 21 Mar 2005
ACCESSION NUMBER: 2005:244636 HCAPLUS Full-text
DOCUMENT NUMBER: 142:456413
TITLE: Depsipeptide (FR901228) Enhances the Cytotoxic Activity of TRAIL by Redistributing TRAIL Receptor

to Membrane Lipid Rafts
AUTHOR(S): VanOosten, Rebecca L.; Moore, Jill M.; Ludwig, Aaron T.; Griffith, Thomas S.
CORPORATE SOURCE: Department of Urology, University of Iowa, Iowa City, IA, 52242-1089, USA
SOURCE: Molecular Therapy (2005), 11(4), 542-552
CODEN: MTOHCK; ISSN: 1525-0016
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB TRAIL (TNF-related apoptosis-inducing ligand) induces apoptosis in various tumor cell types and is under investigation as a cancer therapeutic. The development of a recombinant adenovirus encoding the full-length human TRAIL gene (Ad5- TRAIL) replaces the need for large quantities of soluble TRAIL protein in tumor suppressive therapies . However, the full potential of Ad5-TRAIL has not yet been maximized. Recent investigation of a histone deacetylase inhibitor, depsipeptide (FR901228), has demonstrated that it increases cellular susceptibility to adenovirus infection and augments adenoviral transgene expression. Thus, studies were initiated to evaluate the ability of depsipeptide to enhance the cytotoxic activity of Ad5-TRAIL against human prostate tumor cells. In vitro, depsipeptide increased expression of coxsackie-adenovirus receptor, leading to increased adenoviral infection and transgene expression. Addnl., tumor cell killing by Ad5-TRAIL was higher following depsipeptide pretreatment. More surprisingly, depsipeptide also increased prostate tumor cell sensitivity to TRAIL-induced apoptosis. Investigation into the mechanism responsible for increased TRAIL responsiveness revealed increased levels of TRAIL-R1 and -R2 in membrane lipid rafts following depsipeptide treatment. These results indicate that depsipeptide is a potent agent for enhancing the activity of Ad5- TRAIL by multiple mechanisms, allowing for a more efficient use of Ad5-TRAIL as an antitumor therapy .
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 19 Aug 2004
ACCESSION NUMBER: 2004:674556 HCAPLUS Full-text
DOCUMENT NUMBER: 141:218497
TITLE: Histone deacetylase inhibitors upregulate death receptor 5/TRAIL-R2 and sensitize apoptosis induced by TRAIL/APO2-L in human malignant tumor cells
AUTHOR(S): Nakata, Susumu; Yoshida, Tatsushi; Horinaka, Mano; Shiraishi, Takumi; Wakada, Miki; Sakai, Toshiyuki
CORPORATE SOURCE: Department of Molecular-Targeting Cancer Prevention, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto, 602-8566, Japan
SOURCE: Oncogene (2004), 23(37), 6261-6271
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Death receptor 5 (DR5) is a receptor for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). TRAIL is a promising candidate for cancer therapeutics due to its ability to induce apoptosis selectively in cancer cells. Here, we report that histone deacetylase inhibitors (HDACIs) such as trichostatin A (TSA), sodium butyrate, and suberoylanilide hydroxamic acid (SAHA) upregulated DR5 expression in

various human malignant tumor cells. An RNase protection assay demonstrated that HDACIs induced DR5 mRNA markedly but not that of other death receptor family members in Jurkat cells. HDACIs increased DR5 mRNA and protein in a dose- and time-dependent manner. We also show TSA increased DR5 promoter activity using a luciferase promoter assay. Furthermore, we demonstrated that HDACIs strongly sensitized exogenous soluble recombinant human TRAIL-induced apoptosis synergistically in Jurkat and HL-60 cells that were tolerant to TRAIL alone. The combined use of HDACIs and TRAIL in suboptimal concns. induced Bid cleavage and activation of caspase-8, -10, -3, and -9. Human recombinant DR5/Fc chimera protein, zVAD-fmk pan-caspase inhibitor, and caspase-8 and -10 inhibitors efficiently reduced apoptosis induced by cotreatment with HDACIs and TRAIL. Furthermore, TSA did not significantly induce DR5 protein and HDACIs did not enhance TRAIL-induced apoptosis in normal human peripheral blood mononuclear cells. These results suggest that this combined treatment with HDACIs and TRAIL is a promising strategy for new cancer therapeutics.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 33 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 25 Jun 2004
ACCESSION NUMBER: 2004:513487 HCAPLUS Full-text
DOCUMENT NUMBER: 141:65074
TITLE: Histone deacetylase inhibitor enhancement of TRAIL-induced apoptosis for treatment of leukemia
INVENTOR(S): Bhalla, Kapil N.
PATENT ASSIGNEE(S): University of South Florida, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004052292	A2	20040624	WO 2003-US38881	20031208
WO 2004052292	A3	20050519		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003296310	A1	20040630	AU 2003-296310	20031208
US 20070207119	A1	20070906	US 2005-147112	20050606

PRIORITY APPLN. INFO.:			
US 2002-319759P	P	20021206	
WO 2003-US38881	W	20031208	

AB Due to the poor long-term clin. outcome in the adult patients with several forms of acute leukemia novel treatment strategies are needed to overcome resistance and sensitize the leukemia blasts to the extrinsic and intrinsic

pathway of apoptosis. Treatment with LAQ824 and Apo-2L/TRAIL alone has been recognized to induce apoptosis of leukemia blasts but intrinsic mechanisms of resistance limit the antileukemia activity of either agent when administered alone. The inventive method overcomes the resistance to current apoptosis inducing treatments demonstrated by AML and CML-BC cells by concomitantly administering Apo-2L/TRAIL with the histone deacetylase inhibitor LAQ824.

L58 ANSWER 34 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 02 Apr 2004
ACCESSION NUMBER: 2004:268089 HCAPLUS Full-text
DOCUMENT NUMBER: 140:385629
TITLE: Cotreatment with histone deacetylase inhibitor LAQ824 enhances Apo-2L/tumor necrosis factor-related apoptosis inducing ligand-induced death inducing signaling complex activity and apoptosis of human acute leukemia cells
AUTHOR(S): Guo, Fei; Sigua, Celia; Tao, Jianguo; Bali, Purva; George, Prince; Li, Yunqing; Wittmann, Sylvie; Moscinski, Lynn; Atadja, Peter; Bhalla, Kapil
CORPORATE SOURCE: Moffitt Cancer Center and Research Institute, Department of Interdisciplinary Oncology, University of South Florida, Tampa, FL, 33612, USA
SOURCE: Cancer Research (2004), 64(7), 2580-2589
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Present studies demonstrate that treatment with the histone deacetylases inhibitor LAQ824, a cinnamic acid hydroxamate, increased the acetylation of histones H3 and H4, as well as induced p21WAF1 in the human T-cell acute leukemia Jurkat, B lymphoblast SKW 6.4, and acute myelogenous leukemia HL-60 cells. This was associated with increased accumulation of the cells in the G1 phase of the cell cycle, as well as accompanied by the processing and activity of caspase-9 and -3, and apoptosis. Exposure to LAQ824 increased the mRNA and protein expressions of the death receptors DR5 and/or DR4, but reduced the mRNA and protein levels of cellular FLICE-inhibitory protein (c-FLIP). As compared with treatment with Apo-2L/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or LAQ824 alone, pretreatment with LAQ824 increased the assembly of Fas-associated death domain and caspase-8 , but not of c-FLIP, into the Apo-2L/TRAIL -induced death-inducing signaling complex. This increased the processing of caspase-8 and Bcl-2 interacting domain (BID), augmented cytosolic accumulation of the pro-death mols. cytochrome-c, Smac and Omi, as well as led to increased activity of caspase-3 and apoptosis. Treatment with LAQ824 also down-regulated the levels of Bcl-2, Bcl-xL, XIAP, and survivin. Partial inhibition of apoptosis due to LAQ824 or Apo-2L/TRAIL exerted by Bcl-2 overexpression was reversed by cotreatment with LAQ824 and Apo-2L/TRAIL. Significantly, cotreatment with LAQ824 increased Apo-2L/ TRAIL-induced apoptosis of primary acute myelogenous leukemia blast samples isolated from 10 patients with acute myelogenous leukemia. Taken together, these findings indicate that LAQ824 may have promising activity in augmenting Apo-2L/ TRAIL-induced death-inducing signaling complex and apoptosis of human acute leukemia cells.
IT 9076-57-7, Histone deacetylase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; histone deacetylase inhibitor LAQ824 enhances Apo-2L/TNF-related apoptosis inducing ligand-induced death inducing signaling complex activity and apoptosis of human acute leukemia cells)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 35 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 06 Jan 2004
ACCESSION NUMBER: 2004:7908 HCAPLUS Full-text
DOCUMENT NUMBER: 140:246379
TITLE: Simultaneous activation of the intrinsic and extrinsic pathways by histone deacetylase (HDAC) inhibitors and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) synergistically induces mitochondrial damage and apoptosis in human leukemia cells
AUTHOR(S): Rosato, Roberto R.; Almenara, Jorge A.; Dai, Yun; Grant, Steven
CORPORATE SOURCE: Department of Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, USA
SOURCE: Molecular Cancer Therapeutics (2003), 2(12), 1273-1284
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interactions between histone deacetylase (HDAC) inhibitors and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), also known as Apo2 ligand, were examined in human leukemia cells (e.g., U937, Jurkat, and HL-60). Simultaneous exposure of cells to 100-ng/mL TRAIL with either 1-mM sodium butyrate or 2-μM suberoylanilide hydroxamic acid resulted in a striking increase in leukemic cell mitochondrial damage, caspase activation, and apoptosis. Lethal effects were significantly diminished in U937 cells ectopically expressing dominant-neg. caspase-8, dominant-neg. Fas-associated death domain, CrmA (receptor pathway), or Bcl-2 or Bcl-XL (mitochondrial pathway). Anal. of mitochondrial events in U937 cells exposed to TRAIL/ HDAC inhibitors revealed enhanced Bid activation and Bax translocation, loss of mitochondrial membrane potential, and cytoplasmic release of cytochrome c, Smac/DIABLO, and apoptosis-inducing factor. No changes were observed in expression of FLICE-like inhibitory protein, TRAIL receptors, or reactive oxygen species generation. TRAIL/HDAC inhibitor-induced apoptosis triggered caspase-dependent cleavage of p21WAF1/CIP1; moreover, enforced expression of a nuclear localization signal deletant form of p21WAF1/CIP1 significantly diminished lethality. Lastly, p27KIP1, pRb, X-linked inhibitor of apoptosis, and Bcl-2 displayed extensive proteolysis. These findings indicate that coadministration of TRAIL with HDAC inhibitors synergistically induces apoptosis in human myeloid leukemia cells and provide further evidence that simultaneous activation of the extrinsic and intrinsic pathways in such cells leads to a dramatic increase in mitochondrial injury and activation of the caspase cascade.

IT 9076-57-7, Histone deacetylase
179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(simultaneous activation of intrinsic and extrinsic pathways by histone deacetylase (HDAC) inhibitors and TRAIL synergistically induces mitochondrial damage and apoptosis in human leukemia cells)

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 36 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 18 Dec 2003
ACCESSION NUMBER: 2003:985338 HCAPLUS Full-text
DOCUMENT NUMBER: 140:246363
TITLE: FR901228 induces tumor regression associated with induction of Fas ligand and activation of Fas signaling in human osteosarcoma cells
AUTHOR(S): Imai, Tsuyoshi; Adachi, Souichi; Nishijo, Koichi; Ohgushi, Masatoshi; Okada, Masayuki; Yasumi, Takahiro; Watanabe, Ken-ichiro; Nishikomori, Ryuta; Nakayama, Tomitaka; Yonehara, Shin; Toguchida, Junya; Nakahata, Tatsutoshi
CORPORATE SOURCE: Graduate School of Medicine, Department of Pediatrics, Kyoto University, Sakyo-ku, Kyoto, 606-8507, Japan
SOURCE: Oncogene (2003), 22(58), 9231-9242
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the antitumor effects of FR901228, a HDAC inhibitor, on human osteosarcoma cells, in vitro and in vivo to explore its possible utility in the treatment of pediatric bone cancers. FR901228 caused marked growth inhibition with a 50% inhibitory concentration of 1.2-7.3 nM and induction of apoptosis in all eight osteosarcoma cell lines tested. These effects of FR901228 were also observed in vivo xenograft models on BALB/c nude mice, and treatment with 5.6 mg/kg/day resulting in a >70% reduction in the mean final tumor volume compared with the mean initial tumor volume TUNEL assays demonstrated extensive apoptosis in tumor sections of mice treated with FR901228. Induction of apoptosis was preceded by increased expression of Fas ligand (FasL) mRNA, resulting in expression of membrane-bound FasL, which was followed by sequential activation of caspase-8 and -3. The level of apoptosis induction was reduced using a neutralizing anti-FasL antibody and overexpression of either the dominant-neg. FADD or the viral FLICE inhibitory protein. Furthermore, treatment with a suboptimal dose of FR901228 greatly sensitized osteosarcoma cells to agonistic anti-Fas antibody-mediated apoptosis. These findings suggest that FR901228 is a highly promising antitumor agent against osteosarcoma, inducing apoptosis by the activation of the Fas/FasL system.
IT 179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FR901228 induces tumor regression associated with induction of Fas ligand and activation of Fas signaling in human osteosarcoma cells)
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 37 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 29 Oct 2003
ACCESSION NUMBER: 2003:845074 HCAPLUS Full-text
DOCUMENT NUMBER: 140:296984
TITLE: Induction of apoptosis by apicidin, a histone deacetylase inhibitor, via the activation of mitochondria-dependent caspase cascades in human Bcr-Abl-positive leukemia cells
AUTHOR(S): Cheong, June-Won; Chong, So Young; Kim, Ji Yeon; Eom, Ju In; Jeung, Hoi Kyung; Maeng, Ho Young; Lee, Seung Tae; Min, Yoo Hong
CORPORATE SOURCE: College of Medicine, and Department of Internal

Medicine, Yonsei University College of Medicine, Seoul, 120-752, S. Korea
SOURCE: Clinical Cancer Research (2003), 9(13), 5018-5027
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Apicidin, a histone deacetylase inhibitor, is a novel cyclic tetrapeptide that exhibits potent antiproliferative activity against various cancer cell lines. The aim of this study was to examine the potential of apicidin to induce apoptosis in human Bcr-Abl-pos. leukemia cells and to assess the mechanism of apicidin-induced apoptosis. Cells were exposed to various concns. of apicidin for 2-72 h, after which the levels of apoptosis, histone acetylation, mitochondrial damage, caspase activation, and Bcr-Abl expression were assessed. Apicidin induced apoptosis in K562 cells in a concentration- and time-dependent manner. Similarly, apicidin notably induced the apoptosis in the primary leukemic blasts obtained from chronic myelogenous leukemia patients in blast crisis. The acetylated histone H4 levels increased in a concentration-dependent manner in the K562 cells. However, the timing of cell death caused by apicidin did not exactly correlate with the histone deacetylase inhibitory effect. The disruption of the mitochondrial membrane potential, cytochrome c release into the cytosol, and the mitochondrial Bax translocation were notably demonstrated after the apicidin treatment. Apicidin induced the proteolytic cleavage of procaspase-9, -3, -8, and poly(ADP-ribose) polymerase. Pretreatment of the K562 cells with the caspase-3 inhibitor, DEVD-CHO, completely inhibited the apicidin-induced apoptosis, suggesting that apicidin-induced apoptosis was caspase-dependent. The Fas/Fas ligand death receptor pathway was not involved in the apicidin-mediated apoptosis in K562 cells. Pretreatment of the cells with the caspase-9 inhibitor LEHD-fmk abrogated the apicidin- induced cleavage of procaspase-3, -8, and poly(ADP-ribose) polymerase. The p210 Bcr-Abl protein levels were notably decreased after the apicidin treatment, with near complete loss after 48 h. Reverse transcription-PCR assay demonstrated that the Bcr-Abl mRNA level was also remarkably decreased in a time-dependent manner. These results indicate that apicidin effectively induces the apoptosis of Bcr-Abl-pos. leukemia cells through the activation of the mitochondrial pathway-dependent caspase cascades. The down-regulation of Bcr-Abl mRNA might also be one of the mechanisms implicated in the apicidin-mediated apoptosis in the K562 cells. This study provides the rationale to addnl. investigate apicidin as a potential therapeutic agent for the drug-resistant Bcr-Abl-pos. leukemia cells.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 38 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 16 May 2002
ACCESSION NUMBER: 2002:366480 HCAPLUS Full-text
DOCUMENT NUMBER: 137:304390
TITLE: Histone deacetylase inhibitors sensitize human colonic adenocarcinoma cell lines to TNF-related apoptosis inducing ligand-mediated apoptosis
AUTHOR(S): Inoue, Hidekazu; Shiraki, Katsuya; Ohmori, Shigeru; Sakai, Takahisa; Deguchi, Masatoshi; Yamanaka, Takenari; Okano, Hiroshi; Nakano, Takeshi
CORPORATE SOURCE: First Department of Internal Medicine, Mie University School of Medicine, Mie, 514-8507, Japan
SOURCE: International Journal of Molecular Medicine

(2002), 9(5), 521-525
CODEN: IJMMFG; ISSN: 1107-3756
PUBLISHER: International Journal of Molecular Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Histone deacetylase inhibitor (HDAI) induces accumulation of highly acetylated histones by inhibiting the activity of histone deacetylase and inhibits cell proliferation, induces differentiation, and promotes apoptosis. TNF-related apoptosis inducing ligand (TRAIL) induces apoptosis in various human cancer cells, a promising observation because it raises the possibility of a death ligand selective for tumor cells. However, resistance to TRAIL-induced apoptosis was seen in colonic adenocarcinoma cell lines. So we investigated whether human colonic adenocarcinoma cell lines can be sensitized to TRAIL-induced apoptosis by the addition of HDAI. We investigated sensitivity to histone deacetylase inhibitor in colonic adenocarcinoma cell lines using the MTT assay. Cell viability decreased with sodium butyrate (SB) and trichostatin A (TSA) in a dose-dependent manner in LS 180 and HT-29 cells. Nuclear condensation and fragmentation were observed by DAPI staining after 24 h stimulation with SB or TSA in LS 180 cells. We also investigated the combination of HDAI and TNF family members (TRAIL, anti-Fas antibody or TNFα) in colonic adenocarcinoma cell lines. HDAI augmented TNF family-related apoptosis in LS 180 cells and HT-29 cells. HDAI sensitizes human colonic adenocarcinoma cell lines to TRAIL-mediated apoptosis. Thus, HDAI may be useful as an adjuvant agent for TRAIL in the treatment of human colonic adenocarcinomas that are resistant to TRAIL.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 39 OF 39 HCAPLUS COPYRIGHT 2008 ACS on STN
ED Entered STN: 22 Apr 2002
ACCESSION NUMBER: 2002:298819 HCAPLUS Full-text
DOCUMENT NUMBER: 137:210564
TITLE: Suberoylanilide hydroxamic acid (SAHA) overcomes multidrug resistance and induces cell death in P-glycoprotein-expressing cells
AUTHOR(S): Ruefli, Astrid A.; Bernhard, David; Tainton, Kellie M.; Kofler, Reinhard; Smyth, Mark J.; Johnstone, Ricky W.
CORPORATE SOURCE: Cancer Immunology Division, The Peter MacCallum Cancer Institute, East Melbourne, 3002, Australia
SOURCE: International Journal of Cancer (2002), 99(2), 292-298
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Multidrug resistance (MDR) mediated by the ATP-dependent efflux protein P-glycoprotein (P-gp) is a major obstacle to the successful treatment of many cancers. In addition to effluxing toxins, P-gp has been shown to protect tumor cells against caspase-dependent apoptosis mediated by Fas and tumor necrosis factor receptor (TNFR) ligation, serum starvation and UV irradiation However, P-gp does not protect against caspase-independent cell death mediated by granzyme B or pore-forming proteins (perforin, pneumolysin and activated complement). The authors examined the effects of the chemotherapeutic hybrid polar compound suberoylanilide hydroxamic acid (SAHA) on P-gp-expressing MDR human tumor cell lines. In the CEM T-cell line, SAHA, a histone deacetylase inhibitor, induced equivalent death in P-gp-pos. cells compared with P-gp-neg. cells. Cell death was marked by the caspase-independent release of cytochrome c, reactive oxygen species (ROS) production and Bid cleavage that was not

affected by P-gp expression. However, consistent with the authors' previous findings, SAHA-induced caspase activation was inhibited in P-gp-expressing cells. These data provide evidence that P-gp inhibits caspase activation after chemotherapeutic drug treatment and demonstrates that SAHA may be of value for the treatment of P-gp-expressing MDR cancers.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L1 4222979 SEA FILE=REGISTRY ABB=ON PLU=ON ?HYDROXY?/CNS
L2 259102 SEA FILE=REGISTRY ABB=ON PLU=ON ?PROPENAMIDE?/CNS
L3 262916 SEA FILE=REGISTRY ABB=ON PLU=ON ?"INDOL-3-YL"?/CNS
L4 711 SEA FILE=REGISTRY ABB=ON PLU=ON L1(L)L2(L)L3
L5 12 SEA FILE=REGISTRY ABB=ON PLU=ON (TRAIL/CN OR "TRAIL (TUMOR NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND) (52-ASPARAGINE, 82-GLUTAMINE) (HUMAN)"/CN OR "TRAIL (TUMOR NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND) (HUMAN FRAGMENT)"/CN OR "TRAIL RECEPTOR 1/TR4 (HUMAN)"/CN OR "TRAIL RECEPTOR 2 (HUMAN CELL LINE NTERA-2)"/CN OR "TRAIL RECEPTOR 2 (HUMAN GENE DR5)"/CN OR "TRAIL RECEPTOR 2/TR7 (HUMAN)"/CN OR "TRAIL RECEPTOR 3 (HUMAN)"/CN OR "TRAIL RECEPTOR 3/TR5 (HUMAN)"/CN OR "TRAIL RECEPTOR 4/TR10 (HUMAN)"/CN OR "TRAIL RECEPTOR APO-2 (357-LEUCINE) (HUMAN CLONE 27868 PRECURSOR)"/CN OR "TRAIL RECEPTOR APO-2 (357-METHIONINE) (HUMAN CLONE 27868 PRECURSOR)"/CN)
L6 9 SEA FILE=HCAPLUS ABB=ON PLU=ON (HYDROXY(S)INDOL?)(S)(2(W) PROPENAMIDE)
L7 195 SEA FILE=REGISTRY ABB=ON PLU=ON HISTONE DEACETYLASE?/CN
L8 12435 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 OR L6 OR L7 OR HDAI OR HDAC OR HDI OR HISTONE(W)(DEACETYLASE OR DE ACETYLASE)
L9 32923 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR DR4 OR DR5 OR (DECOY OR DEATH)(W)RECEPTOR OR DCR2 OR DCR 2 OR TRAIL OR APO2L OR APO2 OR (APO OR APOPTOS? OR APOPTOT?)(W)(2 OR 2L) OR AGONIST?(3A)ANTIBOD? OR (TNF OR (TUMOUR OR TUMOR)(W)NECROSIS)(5A)(LIGAND OR SUPERFAMIL? OR SUPER FAMIL? OR RECEPTOR)

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L10          136 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8(L)L9
L38       274695 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (TREAT? OR THERAP? OR
                 PREVENT?)(S)((PROLIFERAT? OR PRO LIFERAT?)(3A)(DISEAS? OR
                 DISORDER) OR ?CANCER? OR ?CARCIN? OR ?TUMOUR? OR ?TUMOR?
                 OR ?NEOPLAS? OR AML OR LEUKEMI## OR LEUKAEMI##)
L39           77 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10(L)L38
L40           31 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39(L)(MAMMAL? OR HUMAN)
L45          114 SEA L40
L46           14 SEA FILE=REGISTRY ABB=ON  PLU=ON  "CASPASE-8"?/CN
L47           32 SEA L45(L)(L46 OR (CASP OR CASPASE)(1W) 8 OR FLICE OR
                 (MACH OR MCH5 OR MCH 5)(3A)(PROTEASE OR PROTEINASE))


L1       4222979 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?HYDROXY?/CNS
L2        259102 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?PROPENAMIDE?/CNS
L3        262916 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?"INDOL-3-YL"?/CNS
L4           711 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1(L)L2(L)L3
L6             9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (HYDROXY(S)INDOL?)(S)(2(W)
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L7           195 SEA FILE=REGISTRY ABB=ON  PLU=ON  HISTONE DEACETYLASE?/CN
L8         12435 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR L6 OR L7 OR HDAI OR
                 HDAC OR HDI OR HISTONE(W)(DEACETYLASE OR DE ACETYLASE)
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L13       318585 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ANTIBODIES AND IMMUNOGLOB
                 ULINS"+OLD,PFT/CT
L14          478 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND (L13 OR L12)
L15          353 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND HUMAN/CT
L16       272881 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ANTITUMOR AGENTS"+OLD,PFT
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L17       193859 SEA FILE=HCAPLUS ABB=ON  PLU=ON  NEOPLASM+OLD,PFT/CT
L18        41140 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LEUKEMIA+OLD,PFT/CT
L19         9985 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ACUTE MYELOID LEUKEMIA"+O
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L20         2538 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "DISEASE, ANIMAL (L)
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L21          219 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND ((L16 OR L17 OR
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L22       199042 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "SIGNAL TRANSDUCTION"+OLD,
                 PFT/CT
L23        16484 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "CYCLIN DEPENDENT KINASE
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L24       125051 SEA FILE=HCAPLUS ABB=ON  PLU=ON  APOPTOSIS+OLD,PFT/CT
L41           91 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 AND L24
L42           30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L41 AND (L22 OR L23)
L43           30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L42 AND HUMAN/CT
L49            0 SEA L43


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L2        259102 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?PROPENAMIDE?/CNS
L3        262916 SEA FILE=REGISTRY ABB=ON  PLU=ON  ?"INDOL-3-YL"?/CNS
L4           711 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1(L)L2(L)L3
L5            12 SEA FILE=REGISTRY ABB=ON  PLU=ON  (TRAIL/CN OR "TRAIL
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                 (52-ASPARAGINE, 82-GLUTAMINE) (HUMAN)"/CN OR "TRAIL (TUMOR
                 NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND) (HUMAN
                 FRAGMENT)"/CN OR "TRAIL RECEPTOR 1/TR4 (HUMAN)"/CN OR
                 "TRAIL RECEPTOR 2 (HUMAN CELL LINE NTERA-2)"/CN OR "TRAIL
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RECEPTOR 2 (HUMAN GENE DR5)"/CN OR "TRAIL RECEPTOR 2/TR7 (HUMAN)"/CN OR "TRAIL RECEPTOR 3 (HUMAN)"/CN OR "TRAIL RECEPTOR 3/TR5 (HUMAN)"/CN OR "TRAIL RECEPTOR 4/TR10 (HUMAN)"/CN OR "TRAIL RECEPTOR APO-2 (357-LEUCINE) (HUMAN CLONE 27868 PRECURSOR)"/CN OR "TRAIL RECEPTOR APO-2 (357-METHIONINE) (HUMAN CLONE 27868 PRECURSOR)"/CN)

L6 9 SEA FILE=HCAPLUS ABB=ON PLU=ON (HYDROXY(S)INDOL?)(S)(2(W) PROPENAMIDE)

L7 195 SEA FILE=REGISTRY ABB=ON PLU=ON HISTONE DEACETYLASE?/CN

L8 12435 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 OR L6 OR L7 OR HDAI OR HDAC OR HDI OR HISTONE(W)(DEACETYLASE OR DE ACETYLASE)

L9 32923 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR DR4 OR DR5 OR (DECOY OR DEATH)(W)RECEPTOR OR DCR2 OR DCR 2 OR TRAIL OR APO2L OR APO2 OR (APO OR APOPTOS? OR APOPTOT?)(W)(2 OR 2L) OR AGONIST?(3A)ANTIBOD? OR (TNF OR (TUMOUR OR TUMOR)(W)NECROSIS)(5A)(LIGAND OR SUPERFAMIL? OR SUPER FAMIL? OR RECEPTOR)

L38 274695 SEA FILE=HCAPLUS ABB=ON PLU=ON (TREAT? OR THERAP? OR PREVENT?)(S)((PROLIFERAT? OR PRO LIFERAT?)(3A)(DISEAS? OR DISORDER) OR ?CANCER? OR ?CARCIN? OR ?TUMOUR? OR ?TUMOR? OR ?NEOPLAS? OR AML OR LEUKEMI## OR LEUKAEMI##)

L46 14 SEA FILE=REGISTRY ABB=ON PLU=ON "CASPASE-8"?/CN

L52 598 SEA L8 AND L9

L53 363 SEA L52 AND L38

L54 105 SEA L53 AND (L46 OR (CASP OR CASPASE)(1W) 8 OR FLICE OR (MACH OR MCH5 OR MCH 5)(3A)(PROTEASE OR PROTEINASE))

L55 96 SEA L54 AND (MAMMAL? OR HUMAN)

L56 96 S L47 OR L55

L57 59 DUP REM L56 (37 DUPLICATES REMOVED)

L57 ANSWER 1 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2008:417903 BIOSIS Full-text

DOCUMENT NUMBER: PREV200800417902

TITLE: Mammalian target of rapamycin contributes to the acquired apoptotic resistance of human mesothelioma multicellular spheroids.

AUTHOR(S): Barbone, Dario; Yang, Tsung-Ming; Morgan, Jeffrey R.; Gaudino, Giovanni; Broaddus, V. Courtney [Reprint Author]

CORPORATE SOURCE: Univ Calif San Francisco, San Francisco Gen Hosp, Lung Biol Ctr, 1001 Potrero Ave,Bldg 1,Rm 150, San Francisco, CA 94110 USA
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SOURCE: Journal of Biological Chemistry, (MAY 9 2008) Vol. 283, No. 19, pp. 13021-13030.
CODEN: JBCHA3. ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 31 Jul 2008
Last Updated on STN: 31 Jul 2008

AB When grown as three-dimensional structures, tumor cells can acquire an additional multicellular resistance to apoptosis that may mimic the chemoresistance found in solid tumors. We developed a multicellular spheroid model of malignant mesothelioma to investigate molecular mechanisms of acquired apoptotic resistance. We found that mesothelioma cell lines, when grown as multicellular spheroids, acquired resistance to a variety of apoptotic stimuli, including combinations of tumor necrosis factor-related

apoptosis-inducing ligand (TRAIL), ribotoxic stressors, histone deacetylase, and proteasome inhibitors, that were highly effective against mesothelioma cells when grown as monolayers. Inhibitors of the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway, particularly rapamycin, blocked much of the acquired resistance of the spheroids, suggesting a key role for mTOR. Knockdown by small interference RNA of S6K, a major downstream target of mTOR, reproduced the effect of rapamycin, thereby confirming the role of mTOR and of S6K in the acquired resistance of three-dimensional spheroids. Rapamycin or S6K knockdown increased TRAIL-induced caspase-8 cleavage in spheroids, suggesting initially that mTOR inhibited apoptosis by actions at the death receptor pathway; however, isolation of the apoptotic pathways by means of Bid knockdown ablated this effect showing that mTOR actually controls a step distal to Bid, probably at the level of the mitochondria. In sum, mTOR and S6K contribute to the apoptotic resistance of mesothelioma cells in three-dimensional, not in two-dimensional, cultures. The three-dimensional model may reflect a more clinically relevant in vitro setting in which mTOR exhibits anti-apoptotic properties.

L57 ANSWER 2 OF 59 MEDLINE on STN
ACCESSION NUMBER: 2008276704 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 18377872
TITLE: Quercetin augments TRAIL-induced apoptotic death: involvement of the ERK signal transduction pathway.
AUTHOR: Kim Young-Ho; Lee Dae-Hee; Jeong Jae-Hoon; Guo Zong Sheng; Lee Yong J
CORPORATE SOURCE: Department of Immunology College of Medicine, Kosin University, Busan 602-702, Republic of Korea.
CONTRACT NUMBER: CA121395 (United States NCI)
CA95191 (United States NCI)
CA96989 (United States NCI)
R01 CA095191-05 (United States NCI)
SOURCE: Biochemical pharmacology, (2008 May 15) Vol. 75, No. 10, pp. 1946-58. Electronic Publication: 2008-03-10. Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200805
ENTRY DATE: Entered STN: 29 Apr 2008
Last Updated on STN: 17 May 2008
Entered Medline: 16 May 2008

AB Combined treatment with quercetin and TRAIL induced cytotoxicity and enhanced annexin V staining and poly (ADP-ribose) polymerase (PARP) cleavage in human prostate cancer cell lines DU-145 and PC-3. These indicators of apoptosis resulted from the activation of caspase-8 , -9, and -3. Although the expression levels of FLIPs, cIAP1, cIAP2, and the Bcl-2 family were not changed in quercetin-treated cells, significant downregulation of survivin occurred. Knockdown survivin by siRNA significantly increased TRAIL-induced apoptosis. We hypothesized that quercetin-induced activation of MAPK (ERK, p38, JNK) is responsible for downregulation of survivin gene expression. To test this hypothesis, we selectively inhibited MAPK during treatment with quercetin. Our data demonstrated that inhibitor of ERK (PD98059), but not p38 MAPK (SB203580) or JNK (SP600125), significantly maintained the intracellular level of survivin during treatment with quercetin. Interestingly, PD98059

also prevented quercetin-induced deacetylation of histone H3. Data from survivin promoter activity assay suggest that the Sp1 transcription factor binds to the survivin promoter region and quercetin inhibits its binding activity through deacetylation of histone H3. Quercetin-induced activation of the ERK-MSK1 signal transduction pathway may be responsible for deacetylation of histone H3. Taken together, our findings suggest that quercetin enhances TRAIL induced apoptosis by inhibition of survivin expression, through ERK-MSK1-mediated deacetylation of H3.

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ACCESSION NUMBER: 2008198122 EMBASE Full-text
TITLE: Valproic acid sensitizes K562 erythroleukemia cells to TRAIL/Apo2L-induced apoptosis.
AUTHOR: Iacomino, Giuseppe (correspondence); Medici, Maria Cristina; Russo, Gian Luigi
CORPORATE SOURCE: Institute of Food Sciences, National Research Council, Avellino, Italy. piacomino@isa.cnr.it
AUTHOR: Iacomino, Giuseppe (correspondence)
CORPORATE SOURCE: Istituto di Scienze dell'Alimentazione, CNR, Via Roma 52 A/C, 83100 Avellino, Italy. piacomino@isa.cnr.it
SOURCE: Anticancer Research, (Mar 2008) Vol. 28, No. 2 A, pp. 855-864.
Refs: 63
ISSN: 0250-7005 CODEN: ANTRD4
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jun 2008
Last Updated on STN: 3 Jun 2008

AB Background: Selectively targeting death receptors to trigger apoptosis in cancer cells appears ideal in cancer therapy. The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L) is of great interest since it has been shown to predominantly kill cancer cells without toxic effects on normal counterparts, thus representing a promising anticancer agent. However, resistance towards TRAIL/Apo2L treatment has also been described. To overcome this obstacle, co-administration of TRAIL/Apo2L plus several compounds, including histone deacetylase inhibitors (HDACi), has been attempted as a strategy to restore cancer cell sensitivity to TRAIL-induced apoptosis. In recent years, the clinical application of HDACi has been largely explored for their ability to modulate gene transcription, block cell division cycle, inhibit cell proliferation, induce cellular differentiation and apoptosis. Materials and Methods: The ability of valproic acid (VPA), a well-known HDACi, to sensitise the K562 cell line, derived from a human leukemia, to TRAIL/Apo2L-mediated apoptosis was evaluated. VPA was selected since it is currently used in clinical practice and its pharmacokinetic, pharmacodynamic and bioavailability are known. Results: When applied with TRAIL /Apo2L, VPA increased cell death and caspase-3 activity by 4-fold compared to the treatment with TRAIL/Apo2L alone. VPA sensitized K562 cells to TRAIL/Apo2L -mediated apoptosis by increasing the expression of DR4 and DR5 by 3- and 14-fold respectively. In addition, VPA per se, in the absence of TRAIL/Apo2L, reduced the expression of antiapoptotic factors, such as c-FLPs, associated with DISC, and Bcl-2/Bcl-X(L), associated with mitochondria, acting

on both extrinsic and intrinsic apoptotic pathways. Conclusion: Our results demonstrated the ability of VPA to sensitize TRAIL/ Apo2L-resistant cells to apoptosis, thus providing an attractive approach for the treatment of leukemias and other proliferative malignancies.

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ACCESSION NUMBER: 2008201719 EMBASE Full-text
TITLE: Modulation of death receptors by cancer therapeutic agents.
AUTHOR: Elrod, Heath A.; Sun, Shi-Yong (correspondence)
CORPORATE SOURCE: Department of Hematology and Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, United States. shi-yong.sun@emoryhealthcare.org
AUTHOR: Sun, Shi-Yong (correspondence)
CORPORATE SOURCE: Winship Cancer Institute, Emory University School of Medicine, 1365-C Clifton Road, C3088, Atlanta, GA 30322, United States. shi-yong.sun@emoryhealthcare.org
SOURCE: Cancer Biology and Therapy, (Feb 2008) Vol. 7, No. 2, pp. 163-173.
Refs: 157
ISSN: 1538-4047 E-ISSN: 1555-8576
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 May 2008
Last Updated on STN: 21 May 2008

AB Death receptors are important modulators of the extrinsic apoptotic pathway. Activating certain death receptors such as death receptors for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (i.e., DR4 and DR5) selectively kills cancer cells via induction of apoptosis while sparing normal cells. Thus, soluble recombinant TRAIL and agonistic antibodies to DR4 or DR5 have progressed to phase I and phase II clinical trials. Many cancer therapeutic drugs including chemotherapeutic agents have been shown to induce the expression or redistribution at the cell surface of death receptors including TRAIL death receptors. In addition, chemotherapeutic agents have also been shown to enhance induction of apoptosis by TRAIL or agonistic antibodies or overcome cell resistance to TRAIL or agonistic antibodies. Targeted induction of apoptosis by activation of the death receptor-mediated extrinsic apoptotic pathway should be an ideal therapeutic strategy to eliminate cancer cells. Therefore, death receptors, particularly TRAIL death receptors, have emerged as an important cancer therapeutic target. This article will focus on reviewing and discussing the modulation of death receptors by cancer therapeutic agents and its implications in cancer therapy. .COPYRGT.2008 Landes Bioscience.

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ACCESSION NUMBER: 2008117920 EMBASE Full-text
TITLE: Modulation of TRAIL-induced apoptosis by

HDAC inhibitors.
AUTHOR: Fulda, Simone (correspondence)
CORPORATE SOURCE: University Children's Hospital, Eythstr.24, D-89075 Ulm, Germany. simone.fulda@uniklinik-ulm.de
SOURCE: Current Cancer Drug Targets, (Mar 2008) Vol. 8, No. 2, pp. 132-140.
Refs: 100
ISSN: 1568-0096 CODEN: CCDTB9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 2008
Last Updated on STN: 2 Apr 2008

AB Triggering apoptosis, the cell's intrinsic death program, is a promising approach for cancer therapy. TNF-related apoptosis-inducing ligand (TRAIL), a member of the TNF superfamily of death inducing ligands, is of special interest for cancer therapy, since TRAIL has been shown to predominantly kill cancer cells, while sparing normal cells. However, since many cancers fail to undergo apoptosis in response to TRAIL treatment, TRAIL-based combination therapies have been developed for cancer-cell specific sensitization towards TRAIL. Chromatin remodelling plays an important role in gene regulation and aberrant architecture of the chromatin has been implicated in tumor formation and progression. In recent years, HDAC inhibitors (HDACI) that reverse aberrant epigenetic changes have emerged as a potential strategy to sensitize cancer cells for TRAIL-induced apoptosis. Synergistic tumor cell death has been reported in a variety of human cancers using different HDACI together with TRAIL. Here, recent advances in the understanding of the molecular events that underlie the synergistic interaction of HDACI and TRAIL are discussed as well as how this knowledge can be translated into the design of cancer-selective novel therapeutics. .COPYRGT. 2008 Bentham Science Publishers Ltd.

L57 ANSWER 6 OF 59 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2008078462 EMBASE Full-text
TITLE: Cellular FLICE-like inhibitory protein (C-FLIP): A novel target for cancer therapy.
AUTHOR: Safa, Ahmad R. (correspondence); Day, Travis W.; Wu, Ching-Huang
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Indiana University Cancer Center, Indiana University School of Medicine, 1044 W. Walnut St., Indianapolis, IN 46202, United States. asafa@iupui.edu
AUTHOR: Safa, Ahmad R. (correspondence)
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Indiana University Cancer Center, 1044 W. Walnut St. R4-119, Indianapolis, IN 46202, United States. asafa@iupui.edu
SOURCE: Current Cancer Drug Targets, (Feb 2008) Vol. 8, No. 1, pp. 37-46.
Refs: 129
ISSN: 1568-0096 CODEN: CCDTB9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer

029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Mar 2008
Last Updated on STN: 4 Mar 2008

AB Cellular FLICE-like inhibitory protein (c-FLIP) has been identified as a protease-dead, procaspase-8-like regulator of death ligand-induced apoptosis, based on observations that c-FLIP impedes tumor necrosis factor-α (TNF-α), Fas-L, and TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis by binding to FADD and/or caspase- 8 or -10 in a ligand-dependent fashion, which in turn prevents death-inducing signaling complex (DISC) formation and subsequent activation of the caspase cascade. c-FLIP is a family of alternatively spliced variants, and primarily exists as long (c-FLIP (L)) and short (c-FLIP(S)) splice variants in human cells. Although c-FLIP has apoptogenic activity in some cell contexts, which is currently attributed to heterodimerization with caspase- 8 at the DISC, accumulating evidence indicates an anti-apoptotic role for c-FLIP in various types of human cancers. For example, small interfering RNAs (siRNAs) that specifically knocked down expression of c-FLIP(L) in diverse human cancer cell lines, e.g., lung and cervical cancer cells, augmented TRAIL-induced DISC recruitment, and thereby enhanced effector caspase stimulation and apoptosis. Therefore, the outlook for the therapeutic index of c-FLIP-targeted drugs appears excellent, not only from the efficacy observed in experimental models of cancer therapy, but also because the current understanding of dual c-FLIP action in normal tissues supports the notion that c-FLIP-targeted cancer therapy will be well tolerated. Interestingly, Taxol, TRAIL, as well as several classes of small molecules induce c-FLIP downregulation in neoplastic cells. Efforts are underway to develop small-molecule drugs that induce c-FLIP downregulation and other c-FLIP-targeted cancer therapies. In this review, we assess the outlook for improving cancer therapy through c-FLIP-targeted therapeutics. .COPYRGT. 2008 Bentham Science Publishers Ltd.

L57 ANSWER 7 OF 59 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2008207062 EMBASE Full-text
TITLE: TRAIL receptor-targeted therapeutics: Resistance mechanisms and strategies to avoid them.
AUTHOR: Thorburn, Andrew (correspondence)
CORPORATE SOURCE: Department of Pharmacology, University of Colorado Denver, School of Medicine, Aurora, CO 80010, United States. Andrew.Thorburn@uchsc.edu
AUTHOR: Behbakht, Kian; Ford, Heide
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Colorado Denver, School of Medicine, Aurora, CO 80010, United States.
SOURCE: Drug Resistance Updates, (Feb 2008) Vol. 11, No. 1-2, pp. 17-24.
Refs: 95
ISSN: 1368-7646 CODEN: DRUPFW
PUBLISHER IDENT.: S 1368-7646(08)00016-2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Jun 2008

Last Updated on STN: 18 Jun 2008

AB Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors are attractive therapeutic targets in cancer because agents that activate these receptors directly induce tumor cell apoptosis and have low toxicity to normal tissues. Consequently, several different drugs that target these receptors (recombinant TRAIL and various agonistic antibodies that activate one of the two TRAIL receptors) have been developed and are being tested in human clinical trials. However, in vitro and in vivo data suggest that resistance to these agents may limit their clinical effectiveness. In this review, we discuss recent findings about some of the ways these resistance mechanisms arise, potential biomarkers to identify TRAIL resistance in patients (Six1, GALNT14, XIAP, certain microRNAs) and potential ways to circumvent resistance and resensitize tumors. .COPYRGT. 2008 Elsevier Ltd. All rights reserved.

L57 ANSWER 8 OF 59 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2007107895 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17257681
TITLE: Regulation of the resistance to TRAIL-induced apoptosis in human primary T lymphocytes: role of NF-kappaB inhibition.
AUTHOR: Morales Jorge Carlos; Ruiz-Magana Maria Jose; Ruiz-Ruiz Carmen
CORPORATE SOURCE: Departamento de Bioquimica y Biologia Molecular 3 e Inmunologia, Facultad de Medicina, Universidad de Granada, Avda. de Madrid 11, 18012 Granada, Spain.
SOURCE: Molecular immunology, (2007 Apr) Vol. 44, No. 10, pp. 2587-97. Electronic Publication: 2007-01-25. Journal code: 7905289. ISSN: 0161-5890.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200706
ENTRY DATE: Entered STN: 21 Feb 2007
Last Updated on STN: 2 Jun 2007
Entered Medline: 1 Jun 2007

AB Several combined strategies have been recently proposed to overcome the resistance to tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) showed by some tumor cells, thus improving the use of this death ligand in antitumor therapy. However, the molecular mechanisms of the tumor selective activity of TRAIL are not completely understood and hence the effects of the combined therapy on normal cells are unknown. Here, we have studied the resistance of primary T lymphocytes to TRAIL-mediated apoptosis. No significant differences were found in the expression of proteins involved in TRAIL-mediated apoptosis between resting and activated T cells. The low expression of death receptors TRAIL-R1/-R2 as well as the high levels of the antiapoptotic proteins TRAIL-R4 and cellular Fas-associated death domain-like IL-1beta-converting enzyme-inhibitory protein (c-FLIP) may explain the lack of caspase-8 activation observed upon TRAIL treatment in both cell types. We have also analyzed the effect of different sensitizing agents such as genotoxic drugs, phosphatidylinositol-3 kinase (PI3K) inhibitors, proteasome inhibitors, microtubule depolymerizing agents, histone deacetylase inhibitors (HDACi), and NF-kappaB inhibitors. Although some of them induced T cell death, only NF-kappaB inhibitors sensitized activated T cells to TRAIL-induced apoptosis, maybe through the regulation of the antiapoptotic proteins TRAIL-R4, c-FLIP(S) and members of the inhibitors of apoptosis proteins (IAP) family. These results question the safety of the combined treatments with TRAIL and NF-kappaB inhibitors against tumors.

L57 ANSWER 9 OF 59 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2007355905 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17462628
TITLE: Membrane expression of DR4, DR5 and caspase-8 levels, but not Mcl-1, determine sensitivity of human myeloma cells to Apo2L/TRAIL.
AUTHOR: Gomez-Benito Maria; Martinez-Lorenzo Maria Jose; Anel Alberto; Marzo Isabel; Naval Javier
CORPORATE SOURCE: Departamento de Bioquimica y Biologia Molecular y Celular, Facultad de Ciencias, Universidad de Zaragoza, Zaragoza, Spain.
SOURCE: Experimental cell research, (2007 Jul 1) Vol. 313, No. 11, pp. 2378-88. Electronic Publication: 2007-03-30. Journal code: 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200708
ENTRY DATE: Entered STN: 19 Jun 2007
Last Updated on STN: 18 Aug 2007
Entered Medline: 17 Aug 2007

AB The improved recombinant form of the death ligand Apo2L/ TRAIL (Apo2L/TRAIL.0) is not cytotoxic for normal human cells and is a good candidate for the therapy of multiple myeloma (MM), a B-cell neoplasia that remains incurable. We have analyzed the molecular determinants of myeloma sensitivity to Apo2L/TRAIL.0 in a number of MM cell lines, the mechanisms of resistance and a possible way of overcoming it. Expression of one death receptor for Apo2L/TRAIL (DR4 or DR5) is sufficient to transduce death signals, though DR5 was more efficient when both receptors were present. Membrane expression of decoy receptors (DcR1, DcR2) and intracellular levels of c-FLIP(L), XIAP and Mcl-1 were not predictive of resistance to Apo2L/TRAIL. Inhibition of Mcl-1 degradation did not prevent Apo2L/ TRAIL-induced apoptosis. In IM-9 cells, resistance was associated to a reduced caspase-8 expression. U266 cells, though expressing significant levels of DR4 and caspase-8, were nevertheless resistant to Apo2L/TRAIL. This resistance could be overcome by co-treatment with valproic acid (VPA), a histone deacetylase inhibitor. VPA caused the redistribution of DR4 to plasma membrane lipid rafts and restored DR4 signaling. Overexpression of Mcl-1 in U266 cells did not prevent Apo2L/TRAIL cytotoxicity in VPA-sensitized cells. These results, taken together, support the possible use of Apo2L/TRAIL.0 in the treatment of MM.

L57 ANSWER 10 OF 59 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2008286532 EMBASE Full-text
TITLE: Epigenetic targets in hematological malignancies: Combination therapies with HDACis and demethylating agents.
AUTHOR: Bishton, Mark; Kenealy, Melita; Prince, H. Miles, Dr. (correspondence)
CORPORATE SOURCE: Peter MacCallum Cancer Center, Department of Haematology, Melbourne, VIC, Australia. miles.prince@petermac.org; mark.bishton@petermac.org; melita.kenealy@petermac.org

AUTHOR: Johnstone, Ricky
CORPORATE SOURCE: Peter MacCallum Cancer Center, Gene Regulation Laboratory, Melbourne, VIC, Australia. ricky.johnstone@petermac.org
AUTHOR: Rasheed, Walid
CORPORATE SOURCE: St. Vincent's Hospital, Department of Haematology, Melbourne, VIC, Australia. walid.rasheed@svhm.org.au
SOURCE: Expert Review of Anticancer Therapy, (Oct 2007) Vol. 7, No. 10, pp. 1439-1449.
Refs: 100
ISSN: 1473-7140 E-ISSN: 1744-8328 CODEN: ERATBJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2008
Last Updated on STN: 27 Jun 2008

AB Chromatin modeling in DNA is fundamental to gene expression, DNA repair and replication. Methylation of promoter regions of tumor-suppressor genes and histone deacetylation leads to gene silencing and transcriptionally repressive chromatin. Histone deacetylase inhibitors and hypomethylating agents allow upregulation of proapoptotic genes and downregulation of antiapoptotic genes, and show significant single-agent anticancer activity, predominantly in cutaneous T-cell lymphoma and myelodysplasia, respectively. Combinations of these drugs are being employed in clinical trials to target multiple biological pathways, with the hope of synergistic pharmacodynamics. Preclinical studies of combinations of these agents with chemotherapy, monoclonal antibodies and small-molecule inhibitors are ongoing and demonstrate synergy in multiple hematollogical cancers, raising the prospect of future treatment for these diseases having a multitargeted approach. .COPYRGT. 2007 Future Drugs Ltd.

L57 ANSWER 11 OF 59 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2007657264 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17982666
TITLE: Differential response of p53 and p21 on HDAC inhibitor-mediated apoptosis in HCT116 colon cancer cells in vitro and in vivo.
AUTHOR: Zopf Steffen; Neureiter Daniel; Bouralexis Steve; Abt Tobias; Glaser Keith B; Okamoto Kinya; Ganslmayer Marion; Hahn Eckhart G; Herold Christoph; Ocker Matthias
CORPORATE SOURCE: Department of Medicine 1, University Hospital Erlangen, D-91054, Erlangen, Germany.
SOURCE: International journal of oncology, (2007 Dec) Vol. 31, No. 6, pp. 1391-402.
Journal code: 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200801
ENTRY DATE: Entered STN: 6 Nov 2007
Last Updated on STN: 16 Jan 2008
Entered Medline: 15 Jan 2008

AB We investigated the effect of a novel histone deacetylase inhibitor, A-423378.0, on the colon carcinoma cell line HCT116 and genetically modified derivatives lacking either p21(cip1/waf1) or p53. HCT116 cell lines were incubated with A-423378.0 at different concentrations for 3-120 h. Cell viability, proliferation and apoptosis rates were determined and verified by western blot, detection of mitochondrial membrane potential breakdown DeltaPsi(m), activation of caspases-3, -8 and cytokeratin 18 cleavage. A subcutaneous xenograft model was established in NMRI mice with daily intraperitoneal injections of 10 mg/kg for 14 days. All three HCT116 cell lines responded to A-423378.0 treatment in a dose- and time-dependent manner via induction of apoptosis as measured by breakdown of DeltaPsi(m) and BrdU incorporation. We identified that A-423378.0 induced the expression of TRAIL and TRAIL receptor, especially TRAIL-R2/hDR5, which was up-regulated in HCT116 cells after treatment with A-423378.0. In vivo, a growth inhibitory effect was observed with HDAC-I treatment, which was paralleled by a down-regulation of PCNA and a concomitant induction of apoptosis. Treatment of wild-type or knock-out HCT116 cells with A-423378.0 exerts potent anti-proliferative and pro-apoptotic effects in vitro and in vivo. A-423378.0 was able to induce apoptosis in both p21(WAF1) and p53 deficient tumour cells, which appeared to be mediated by the intrinsic cell death pathway. Interestingly, the effects of A-423378.0 on the extrinsic cell death pathway through activation of TRAIL and its signalling pathway indicate that A-423378.0 may be a potent new therapeutic compound for the treatment of advanced colorectal cancer.

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ACCESSION NUMBER: 2007089103 EMBASE Full-text
TITLE: Selective inhibition of PED protein expression sensitizes B-cell chronic lymphocytic leukaemia cells to TRAIL-induced apoptosis.
AUTHOR: Garofalo, Michela; Romano, Giulia; Quintavalle, Cristina; Zanca, Ciro; Condorelli, Gerolama (correspondence)
CORPORATE SOURCE: Department of Cellular and Molecular Biology and Pathology, University of Naples Federico, II, Via Pansini 5, 80131 - Naples, Italy. gecondor@unina.it
AUTHOR: Romano, Maria Fiammetta
CORPORATE SOURCE: Dipartimento di Biochimica e Biotecnologie Mediche, Facolta di Medicina e Chirurgia, Universita degli Studi di Napoli Federico II, Naples, Italy.
AUTHOR: Chiurazzi, Federico
CORPORATE SOURCE: Divisione di Ematologia, Facolta di Medicina e Chirurgia, Universita degli Studi di Napoli, Federico II, Naples, Italy.
SOURCE: International Journal of Cancer, (15 Mar 2007) Vol. 120, No. 6, pp. 1215-1222.
Refs: 31
ISSN: 0020-7136 E-ISSN: 1097-0215 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
029 Clinical and Experimental Biochemistry
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 2007
Last Updated on STN: 29 Mar 2007

AB B-cell chronic lymphocytic leukaemia (B-CLL) cells fail to undergo apoptosis. The mechanism underlying this resistance to cell death is still largely unknown. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) effectively kills tumour cells but not normal cells, and thus represents an attractive tool for the treatment of cancer. Unfortunately, lymphocytes from B-CLL patients are resistant to TRAIL-mediated apoptosis. Thus, we aimed to study the involvement of PED, a DED-family member with a broad antiapoptotic action, in this resistance. We demonstrate that B lymphocytes obtained from patients with B-CLL express high levels of PED. Treatment of B-CLL cells with specific PED antisense oligonucleotides, a protein synthesis inhibitor or HDAC inhibitors, induced a significant downregulation of PED and sensitized these cells to TRAIL-induced cell death. These findings suggest a direct involvement of PED in resistance to TRAIL -induced apoptosis in B-CLL. It also identifies this DED-family member as a potential therapeutic target for this form of leukaemia. .COPYRGT. 2006 Wiley-Liss, Inc.

L57 ANSWER 13 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2008:218361 BIOSIS Full-text
DOCUMENT NUMBER: PREV200800218403
TITLE: Valproic acid induces apoptosis in chronic lymphocytic leukemia cells by targeting several pro- and anti-apoptotic genes.
AUTHOR(S): Starnatopoulos, Basile [Reprint Author]; Meuleman, Nathalie; Kentos, Alain; Hermans, Philippe; Martial, Philippe; Bron, Dominique; Lagneaux, Laurence
CORPORATE SOURCE: Univ Brussels, Inst Jules Bordet, Lab Expt Hematol, Brussels, Belgium
SOURCE: Blood, (NOV 16 2007) Vol. 110, No. 11, Part 1, pp. 921A.
Meeting Info.: 49th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 08 -11, 2007. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Mar 2008
Last Updated on STN: 26 Mar 2008

AB Histone deacetylase inhibitors have been shown to modulate the cell cycle, to induce apoptosis and to sensitize cancer cells to other chemotherapeutics. Among These inhibitors, valproic acid (VPA), an antiepileptic drug, is being. discussed as a promising novel anti-cancer drug. Chronic Lymphocytic Leukemia (CLL) is a clinically heterogeneous disease remaining incurable despite introducing new promising treatments. The effects of VPA and its mechanism of action were evaluated on mononuclear cells isolated from 40 CLL patients. Exposure of CLL cells to increased,doses of VPA (0.5-5mM) leads to a dose-dependent cytotoxicity and apoptosis in all CLL patients. VPA treatment induced apoptotic changes in CLL cells including phosphatidylserine externalization and DNA fragmentation. The mean apoptotic rates were similar between GHV mutated and immolated patients, the latter presenting a more aggressive clinical course. VPA induced apoptosis via the c) trinsic pathway involving engagement of the caspase -8-dependent cascade. Interestingly, VPA increased the sensitivity of leukemic cells to tumor necrosis factor-related apoptosis inducing ligand (TRAIL) even among resistant patients. Moreover, VPA at Physiological concentration of 1 mM can significantly increase the in vitro cytotoxic effects of fludarabine,bortezomib and the natural product honokiol allowing the reduction of effective concentration 50% (EC50). In order to understand the early mechanism of action of VPA, we investigated gene

expression profiles of 14 CLL-patient samples (7 with a good prognosis and 7 with a bad prognosis regarding IGHV mutational status and Zap-70 expression) treated in vitro during 4 hours with a physiological dose (1 mM) of VPA and compared with their untreated counterpart using Affymetrix technology. No difference in gene modulation was observed between poor and good prognosis patients after VPA treatment. Modulation of several pro- and anti-apoptotic mRNA expression was confirmed by a real-time reverse transcription-PCR The molecular analysis of the apoptotic machinery involved in VPA response revealed the up-regulation of APAF1 (5.5 fold, P<0.0001),BNIP3 (2.2 fold, P=0.0006), PTEN (1.9 fold, P=0.0002), CASP6 (2.5 fold, P<0.0001) an.] the down-regulation of CFLAR/FLIP (2.0 fold, P<0.0001), BCL2 (1.6 fold, P=0.0222), AVEN (1.9 fold, P<0.0001), BIRC4/XIAP (1.7 fold, P<0.0001) and BIRC1/NAIP (1.6 fold, P=0.0007). In conclusion, VPA induced apoptosis of CLL cells at clinically relevant concentration by selective activation of the caspase -8 (extrinsic) pathway and by targeting several pro- and anti-apoptotic genes. Therefore, the combined application of VPA with other drugs might be considered as a potential strategy for CLL treatment.

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ACCESSION NUMBER: 2007:579399 BIOSIS Full-text
DOCUMENT NUMBER: PREV200700579317
TITLE: Histone deacetylase inhibitors induce cell death and enhance the apoptosis-inducing activity of TRAIL in Ewing's sarcoma cells.
AUTHOR(S): Sonnemann, Juergen; Dreyer, Linn; Hartwig, Maite; Palani, Chithra D.; Hong, Le Thi Thu; Klier, Ulrike; Broeker, Barbara; Voelker, Uwe; Beck, James F. [Reprint Author]
CORPORATE SOURCE: Zentrum Kinder and Jungendmed, Abt Padiatr Onkol and Hamatol, Soldmannstr 15, D-17475 Greifswald, Germany beck@uni-greifswald.de
SOURCE: Journal of Cancer Research and Clinical Oncology, (NOV 2007) Vol. 133, No. 11, pp. 847-858. CODEN: JCROD7. ISSN: 0171-5216.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Nov 2007
Last Updated on STN: 14 Nov 2007

AB Purpose The present in vitro study was conducted to evaluate the effects of the histone deacetylase inhibitors (HDIs) suberoyl anilide hydroxamic acid (SAHA), sodium butyrate (NaB) and MS-275 applied as single agents or in combination with TRAIL in Ewing's sarcoma.Methods Cytotoxic activities were assessed by cytofluorometric analysis of propidium iodide uptake, DNA fragmentation and mitochondrial depolarisation as well as by measuring caspase-9 and -3 activities. Cell-surface expression of TRAIL receptors was determined by cytofluorometry, and histone H4 acetylation was assessed by western blot.Results All three HDIs potently induced cell death in the two cell lines explored, SK-ES-1 and WE-68. However, they seemed to differ in their modes of action. SAHA and NaB induced mitochondrial depolarisation as well as caspase-9 and -3 activities, and their cytotoxic effects could be significantly reduced by the pan-caspase inhibitor z-VAD-fmk. MS-275 was a much weaker inducer of caspase-9 and -3 activities as well as mitochondrial injury; consistently, z-VAD-fmk had little effect on MS-275-mediated activities. Combined treatment of HDIs and TRAIL led to an additive effect in SK-ES-1 cells and a supra-additive effect in WE-68 cells. Yet, HDIs did not increase cell-surface expression of TRAIL receptor 2, but rather decreased it. Selective inhibition of caspase -8 in WE-68 cells and HDI treatment of CADO-ES-1 cells, a Ewing's sarcoma cell line deficient in caspase- 8 expression,

revealed that caspase-8 was not required for HDI-mediated apoptosis.Conclusions These results suggest that HDIs may be considered as a novel treatment strategy for Ewing's sarcoma either applied as monotherapy or in combination with TRAIL.

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ACCESSION NUMBER: 2008:217749 BIOSIS Full-text
DOCUMENT NUMBER: PREV200800217791
TITLE: KD7150, a novel mercaptoketone-based HDAC inhibitor, exerts potent anti-multiple myeloma effects in vitro and in vivo by induction of DNA damage and mitochondrial signaling.
AUTHOR(S): Feng, Rentian [Reprint Author]; Ma, Huihui; Hassig, Christian A.; Payne, Joseph E.; Smith, Nicholas D.; Mapara, Markus Y.; Hager, Jeffrey H.; Lentzsch, Suzanne
CORPORATE SOURCE: Univ Pittsburgh, Ctr Canc, Dept Med, Div Hematol Oncol, Pittsburgh, PA 15260 USA
SOURCE: Blood, (NOV 16 2007) Vol. 110, No. 11, Part 1, pp. 743A.
Meeting Info.: 49th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 08 -11, 2007. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Mar 2008
Last Updated on STN: 26 Mar 2008

AB Histone deacetylase (HDAC) inhibitors have emerged as a class of novel and promising anti-cancer agents and their activities are currently being investigated in both the pre-clinical and clinical settings. Using an unbiased, ultrahigh throughput screening system a novel mercaptoketone-based HDAC inhibitor KD5170 was identified. This novel non-hydroxamic acid non-benzamide compound was profiled for its anti-myeloma activity in vitro and in vivo. KD5170 inhibited the proliferation of multiple myeloma (MM) cell lines and the viability of CD138+ primary MM cells by induction of apoptosis. This was accompanied by an increase of acetylation of histories and activation of caspase-3, - 8 and -9. Treatment with KD5170, caused a loss of mitochondrial membrane potential measured by JC-1 staining and resulted in release of apoptogenic factors such as cytochrome c, smac, and AIF from mitochondria. Furthermore, KD5170 induced oxidative stress and oxidative DNA damage in myeloma cells, as evidenced by the, upregulation of heme oxygenase-1 and H2A.X phosphorylation, respectively. Combination of KD5170 with the proteasome inhibitor bortezomib or TNF-related apoptosis-inducing ligand synergistically enhanced the anti-myeloma, activity. Resistance of MM cells to KD5170 was associated with activation of the ERK/MAPK pathway under treatment with KD5170. Pretreatment with the MAPK-inhibitor restored the sensitivity to KD5170, suggesting that the combination of KD5170 with a MAPK inhibitor (U0126) could overcome drug resistance. Growth of myeloma tumor xenografts in KD5170-treated nude mice was significantly inhibited (1401 mm(3)+/- 596 versus 442 mm(3) +/- 221; P =.009) and survival was prolonged (9 days and 17.5 days; P=.0095) compared to vehicle-treated mice: Accordingly, our in vivo data showed that historic acetylation was markedly upregulated in tela in spleen or tumor tissues of the animals treated with KD5170 as early as 2 hours. In conclusion, our data show that KD5170 has anti-myeloma activity in vitro and in vivo, mediated by the induction of apoptosis due to DNA damage and mitochondrial signaling.

L57 ANSWER 16 OF 59 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2007115120 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17195089
TITLE: Histone deacetylase inhibitors enhance Ad5-TRAIL killing of TRAIL -resistant prostate tumor cells through increased caspase-2 activity.
AUTHOR: VanOosten Rebecca L; Earel James K Jr; Griffith Thomas S
CORPORATE SOURCE: Department of Urology, 3204 MERF, University of Iowa, 375 Newton Road, Iowa City, IA 52242-1089, USA.
CONTRACT NUMBER: CA109446 (United States NCI)
SOURCE: Apoptosis : an international journal on programmed cell death, (2007 Mar) Vol. 12, No. 3, pp. 561-71. Electronic Publication: 2006-12-30. Journal code: 9712129. ISSN: 1360-8185.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200706
ENTRY DATE: Entered STN: 27 Feb 2007 Last Updated on STN: 15 Jun 2007 Entered Medline: 14 Jun 2007

AB Interest in TNF-related apoptosis-inducing ligand (TRAIL) as a cancer therapeutic has been high since its first description. Recently, the use of histone deacetylase inhibitors (HDACi) to treat cancer has progressed from the laboratory to the clinic, and the combination of HDACi and TRAIL is very powerful in killing human tumors. Using a panel of prostate tumor cell lines (ALVA-31, DU-145, and LNCaP) with varying TRAIL sensitivity, we examined their sensitization to a recombinant adenovirus encoding TRAIL (Ad5-TRAIL) by sodium butyrate and trichostatin A. HDACi treatment increased coxsackie-adenovirus receptor (CAR) expression, resulting in increased adenoviral infection, and increased TRAIL-mediated killing. In TRAIL-resistant DU-145 cells, HDAC inhibition also decreased protein kinase casein kinase (PKCK) 2 activity, leading to caspase-2 activation. The importance of PKCK2 and caspase-2 in DU-145 sensitization was demonstrated with the PKCK-2-specific inhibitor, which enhanced Ad5-TRAIL-induced death, or the caspase-2-specific inhibitor, zVDVAD, which blocked Ad5-TRAIL -induced death. Thus, our data highlight the connection between HDAC inhibition of PKCK2 activity and tumor cell sensitivity to TRAIL-induced apoptosis. Specifically, HDAC inhibition leads to decreased PCKC2 activity, which is followed by caspase-2 activation and partial cleavage of caspase- 8 that sensitizes the tumor cell to TRAIL.

L57 ANSWER 17 OF 59 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2007486694 EMBASE Full-text
TITLE: Sodium butyrate-dependent sensitization of human colon adenocarcinoma COLO 205 cells to TNF-γ-induced apoptosis.
AUTHOR: Pajak, Beata, Dr. (correspondence); Orzechowski, A.
CORPORATE SOURCE: Department of Physiological Sciences, Faculty of Veterinary Medicine, Warsaw Agricultural University, Nowoursynowska 159, 02-776 Warsaw, Poland. bepaj@wp.pl
SOURCE: Journal of Physiology and Pharmacology, (Aug 2007) Vol. 58, No. SUPPL. 3, pp. 163-176.

Refs: 24
ISSN: 0867-5910 CODEN: JPHPEI
COUNTRY: Poland
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2007
Last Updated on STN: 16 Oct 2007

AB COLO 205 colon adenocarcinoma cells are highly resistant to extrinsic apoptosis induced by immunomodulatory cytokines. One of the antiapoptotic mechanisms is the expression of cFLIP protein, which inhibits TNF-α-induced cell death. The use of metabolic inhibitors, such as sodium butyrate (NaBt), the potent repressor of histone deacetylase, sensitizes tumor cells to TNF-α-mediated apoptosis. The Western-blot analysis revealed that in COLO 205 cells the susceptibility to apoptogenic stimuli results from time-dependent reduction in cFLIP(L) protein assembled with DISC complex. At the same time, the level of transmembrane TNF-α receptor 1 (TNF-R1) was elevated which is consistent with the exaggerated rate of cell death. Since preincubation of COLO 205 cells with N-acetyl-L-cysteine (NAC), or sodium ascorbate (ASC) did not protect cells from combined NaBt- and TNF-α-induced apoptosis, we concluded that deletion of cancer cells is not evoked by oxidative stress. Our results suggest that the combination of TNF-α with NaBt targets antiapoptotic protein(s) and may provide efficient and non-toxic treatment of colon cancer.

L57 ANSWER 18 OF 59 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2007204273 EMBASE Full-text
TITLE: Research advances in apoptosis-mediated cancer therapy: A review.
AUTHOR: Lopez-Beltran, Antonio, Dr. Prof. (correspondence)
CORPORATE SOURCE: Unit of Anatomic Pathology, Cordoba University Medical School, Reina Sofia University Hospital, Cordoba, Spain . em1lobea@uco.es
AUTHOR: MacLennan, Gregory T.
CORPORATE SOURCE: Department of Pathology, Case Western Reserve University, Cleveland, OH, United States.
AUTHOR: De La Haba-Rodriguez, Juan
CORPORATE SOURCE: Oncology Service, Reina Sofia University Hospital, Cordoba, Spain.
AUTHOR: Montironi, Rodolfo
CORPORATE SOURCE: Institute of Pathological Anatomy and Histopathology, Polytechnique University of the Marche Region, Ancona, Italy.
AUTHOR: Cheng, Liang
CORPORATE SOURCE: Departments of Pathology and Laboratory Medicine and Urology, Indiana University School of Medicine, Indianapolis, IN, United States.
AUTHOR: Lopez-Beltran, Antonio, Dr. Prof. (correspondence)
CORPORATE SOURCE: Unit of Anatomic Pathology, Faculty of Medicine, Avenida Menendez-Pidal S/N, E-14004, Cordoba, Spain. em1lobea@uco.es
SOURCE: Analytical and Quantitative Cytology and Histology,

(Apr 2007) Vol. 29, No. 2, pp. 71-78.
Refs: 32
ISSN: 0884-6812 CODEN: AQCHED
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 2007
Last Updated on STN: 7 Jun 2007

AB Apoptosis (programmed cell death) research has received much attention because of its wide-ranging implications in tissue kinetics. The ability of malignant cells to evade apoptosis is a hallmark of cancer, and their resistance to apoptosis constitutes an important clinical problem. Targeting proteins from the apoptotic signaling pathways for cancer therapy is currently an important research strategy, with some compounds entering clinical trials as novel therapeutic drugs in cancer medicine. These compounds may target the apoptosis machinery or may be inhibitors of growth factors that kill tumor cells via apoptosis. This review summarizes current observations in the literature related to recent research developments in apoptosis-mediated cancer therapy. .COPYRGT. Science Printers and Publishers, Inc.

L57 ANSWER 19 OF 59 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2006739496 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17136498
TITLE: Rapid and profound potentiation of Apo2L/TRAIL-mediated cytotoxicity and apoptosis in thoracic cancer cells by the histone deacetylase inhibitor Trichostatin A: the essential role of the mitochondria-mediated caspase activation cascade.
AUTHOR: Reddy Rishindra M; Yeow Wen-Shuz; Chua Alex; Nguyen Duc M; Baras Aris; Ziauddin M Firdos; Shamimi-Noori Susan M; Maxhimer Justin B; Schrump David S; Nguyen Dao M
CORPORATE SOURCE: Section of Thoracic Oncology, Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: Apoptosis : an international journal on programmed cell death, (2007 Jan) Vol. 12, No. 1, pp. 55-71.
Journal code: 9712129. ISSN: 1360-8185.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., INTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200704
ENTRY DATE: Entered STN: 21 Dec 2006
Last Updated on STN: 25 Apr 2007
Entered Medline: 24 Apr 2007

AB Apo2L/TRAIL is actively investigated as a novel targeted agent to directly induce apoptosis of susceptible cancer cells. Apo2L/TRAIL-refractory cells can be sensitized to the cytotoxic effect of this ligand by cytotoxic chemotherapeutics. The aim of this study was to evaluate the in vitro tumoricidal activity of the Apo2L/TRAIL + Trichostatin A in cultured thoracic cancer cells and to elucidate the molecular basis of the synergistic cytotoxicity of this combination. Concurrent exposure of cultured cancer cells

to sublethal concentrations of Apo2L/TRAIL and Trichostatin A resulted in profound enhancement of Apo2L/TRAIL -mediated cytotoxicity in all cell lines regardless of their intrinsic susceptibility to this ligand. This combination was not toxic to primary normal cells. While Apo2L/TRAIL alone or Trichostatin A alone mediated < 20% cell death, 60 to 90% of cancer cells were apoptotic following treatment with TSA + Apo2L/TRAIL combinations. Complete translocation of Bax from the cytosol to the mitochondria compartment was mainly observed in combination-treated cells and this was correlated with robust elevation of caspase 9 proteolytic activity indicative of activation of the mitochondria apoptogenic effect. Profound TSA + Apo2L/TRAIL-mediated cytotoxicity and apoptosis were completely abrogated by either Bcl2 over-expression or by the selective caspase 9 inhibitor, highlighting the essential role of mitochondria-dependent apoptosis signaling cascade in this process. Moreover, increased caspase 8 activity observed in cells treated with the TSA + Apo2L/TRAIL combination was completely suppressed by Bcl-2 over-expression or by the selective caspase 9 inhibitor indicating that the elevated caspase 8 activity in combination-treated cells was secondary to a mitochondria-mediated amplification feedback loop of caspase activation. These finding form the basis for further development of HDAC inhibitors + Apo2L/ TRAIL combination as novel targeted therapy for thoracic malignancies.

L57 ANSWER 20 OF 59 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2006696969 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17051334
TITLE: Bim plays a crucial role in synergistic induction of apoptosis by the histone deacetylase inhibitor SBHA and TRAIL in melanoma cells.
AUTHOR: Gillespie Susan; Borrow Jodie; Zhang Xu Dong; Hersey Peter
CORPORATE SOURCE: Immunology and Oncology Unit, Room 443, Newcastle Misericordiae Hospital, NSW, Australia.
SOURCE: Apoptosis : an international journal on programmed cell death, (2006 Dec) Vol. 11, No. 12, pp. 2251-65. Journal code: 9712129. ISSN: 1360-8185.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200703
ENTRY DATE: Entered STN: 1 Dec 2006
Last Updated on STN: 14 Mar 2007
Entered Medline: 13 Mar 2007

AB The wide variation in sensitivity of cancer cells to TRAIL- or histone deacetylase (
HDAC) inhibitor - induced apoptosis precludes successful treatment of cancer with these agents. We report here that TRAIL and SBHA synergistically induce apoptosis of melanoma cells as revealed by quantitative analysis using the normalized isobologram method. This is supported by enhanced activation of caspase-3 and cleavage of its substrates, PARP and ICAD. Co-treatment with SBHA and TRAIL did not enhance formation of the death-inducing signaling complex (DISC) and processing of caspase-8 and Bid, but potentiated activation of Bax and release of Cytochrome C and Smac/DIABLO from mitochondria into the cytosol. SBHA down-regulated Bcl-X(L), Mcl-1 and XIAP, but up-regulated Bax, Bak, and the BH3-only protein Bim(EL). Up-regulation of the latter by SBHA was attenuated by the presence of TRAIL, which was inhibitable by the pan-caspase inhibitor z-VAD-fmk. Inhibition of Bim by siRNA attenuated conformational changes of Bax, mitochondrial apoptotic events, and activation of caspase-3, leading to marked inhibition of the synergy between SBHA and TRAIL. Thus, Bim

plays an essential role in synergistic induction of apoptosis by SBHA and TRAIL in melanoma.

L57 ANSWER 21 OF 59 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2006099923 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16489094
TITLE: Human melanoma cells selected for resistance to apoptosis by prolonged exposure to tumor necrosis factor-related apoptosis-inducing ligand are more vulnerable to necrotic cell death induced by cisplatin.
AUTHOR: Zhang Xu Dong; Wu Jing Jing; Gillespie Susan; Borrow Jodie; Hersey Peter
CORPORATE SOURCE: Immunology and Oncology Unit, Royal Newcastle Hospital, Newcastle, NSW, Australia.
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2006 Feb 15) Vol. 12, No. 4, pp. 1355-64.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 22 Feb 2006
Last Updated on STN: 18 Apr 2006
Entered Medline: 17 Apr 2006

AB PURPOSE: Heterogeneous sensitivity of melanoma cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis may lead to outgrowth of TRAIL-resistant cells and limit successful treatment by TRAIL. The present study aims to better understand the biological characteristics of melanoma cells resistant to TRAIL-induced apoptosis. EXPERIMENTAL DESIGN: We generated TRAIL-resistant melanoma cells by prolonged exposure to TRAIL and characterized the cells in terms of their sensitivity to killing induced by a panel of cytotoxic agents using biological and biochemical methods. RESULTS: TRAIL -resistant melanoma cells are cross-resistant to apoptosis induced by another death ligand FasL, the DNA-damaging agent cisplatin, the histone deacetylase inhibitor suberic bishydroxamate, and the antimicrotubule Vinca alkaloid, vincristine. The apoptotic signaling seemed to be inhibited upstream of mitochondrial apoptotic events and was associated with decreased expression of multiple apoptotic mediators, including pro- caspase-8, Fas-associated death domain, Bid, Bim, p53, and the products of its proapoptotic target genes. Despite being resistant to apoptosis, TRAIL-resistant melanoma cells were more vulnerable to cisplatin-induced nonapoptotic cell death. This was characterized by lack of DNA fragmentation, delayed externalization of phosphatidylserine, caspase and p53 independence, and severe mitochondrial disruption, and was preceded by poly(ADP)ribose polymerase (PARP) activation and depletion of intracellular ATP, indicative of necrotic cell death. Inhibition of PARP activity partially converted the mode of cell death from necrosis to apoptosis. CONCLUSIONS: TRAIL-resistant melanoma cells are cross-resistant to apoptosis induced by various apoptotic stimuli but are more sensitive to nonapoptotic cell death induced by cisplatin. Exploration of chemotherapy-induced nonapoptotic cell death may provide an alternative strategy in overcoming resistance of melanoma cells to TRAIL-induced apoptosis.

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on STN
ACCESSION NUMBER: 2006:588026 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600598652
TITLE: Synergistic interactions between the HbAC inhibitor NVP-LAQ824 and the nucleoside analog fludarabine in human leukemia cells involve ROS generation and modulation of the NF-kB and JNK pathways.
AUTHOR(S): Rosato, Roberto R. [Reprint Author]; Maggio, Sonia C.; Almenara, Jorge A.; Coe, Stefanie; Rahmani, Mohamed; Dai, Yun; Atadja, Peter; Grant, Steven
CORPORATE SOURCE: Novartis Inst Biomed Res, E Hanover, NJ USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2006) Vol. 47, pp. 1095. Meeting Info.: 97th Annual Meeting of the American-Association-for-Cancer-Research (AACR). Washington, DC, USA. April 01 -05, 2006. Amer Assoc Canc Res.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Nov 2006
Last Updated on STN: 8 Nov 2006

L57 ANSWER 23 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:268872 BIOSIS Full-text
DOCUMENT NUMBER: PREV200700260229
TITLE: Emerging of valproic acid as an anti-myeloma agent.
AUTHOR(S): Kitazoe, Kenichi [Reprint Author]; Abe, Masahiro; Choraku, Masahito; Kagawa, Kumiko; Asano, Jin; Takeuchi, Kyoko; Hiasa, Masahiro; Hashimoto, Toshihiro; Ozaki, Shuji; Oda, Asuka; Amou, Hiroe; Matsumoto, Toshio
CORPORATE SOURCE: Univ Tokushima, Grad Sch Hlth Biosci, Dept Med and Bioregulatory Sci, Tokushima 770, Japan
SOURCE: Blood, (NOV 16 2006) Vol. 108, No. 11, Part 1, pp. 993A. Meeting Info.: 48th Annual Meeting of the American-Society-of-Hematology. Orlando, FL, USA. December 09 -12, 2006. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Apr 2007
Last Updated on STN: 25 Apr 2007

AB Multiple myeloma (MM) expands in a manner dependent on the bone marrow microenvironment, and develops devastating bone destruction. MM is still an incurable disease, and preferentially arises in the elderly. Therefore, novel well-tolerated therapeutic alternatives are wanted especially for elderly patients with MM. Valproic acid (VPA), a well-tolerated and safe anti-epileptic agent with extensive clinical experience, has recently been shown to be a class I- and IIa-specific HDAC inhibitor, and induce cytotoxic effects on various types of tumor cells. In the present study, we evaluated the impact of VPA on MM cell growth and survival as well as MM-induced bone marrow microenvironment. VPA reduced viable cell numbers to less than 50 % from the baseline at day 2 in all MM cell lines (5/5) as well as primary CD138-positive MM cells (4/4) tested, and a portion of B cell (215) and T cell (1/3) lines, but not in AML cell lines (0/4) at 100 microg/ml, a therapeutic concentration

for epilepcy, which raises a possibility for VPA as a therapeutic agent against MM. Interestingly, CD138-negative non-MM bone marrow cells remained intact and CFU-GM numbers were not affected by VPA, suggesting tumor-specific actions of VPA. VPA induced death receptor- but not mitochondrial pathway-mediated apoptosis with down-regulation of cellular FLICE-inhibitory protein (c-FLIP) and cleavage of caspase 8 in RPMI8226 MM cells. Furthermore, VPA down-regulated cyclin D1, and up-regulated the cyclin-dependent kinase inhibitor p21(Cip1) with accumulation of MM cells, at G0/G1 phase, suggesting the involvement of cell cycle arrest in anti-proliferation actions of VPA. Notably, A at therapeutically relevant concentrations potentiated the induction of apoptosis by dexamethasone which triggers the release of Smac from mitochondria. However, VPA did not enhance the cytotoxic effects of cell cycle-specific agents including doxorubicine and melphalan. The VPA-induced tumor cell dormancy may reduce the susceptibility of MM cells to such cell cycle-specific agents. In parallel with MM progression, angiogenesis as well as osteoclastogenesis are enhanced in the bone marrow. We previously demonstrated that MM cell-osteoclast (OC) interactions enhance the growth and survival of MM cells as well as angiogenesis. Therefore. we next investigated the effects of VPA on MM cell-OC interactions and angiogenesis. Although VPA showed no significant effects on osteoclastogenesis induced by MM cells. VPA suppressed the growth and survival of RPMI8226 and U266 MM cells in the presence of OCs generated from monocytes to the levels similar to those without OCs. Furthermore, NTA potently inhibited in vitro vascular tubule formation enhanced by conditioned media from co-cultures of MM cells and OCs. Such anti-angiogenic effects of VPA was further potentiated in concert with thalidomide. Collectively, the present study suggests that VPA exerts multi-factorial anti-MM actions and may serve as a novel well-tolerated therapeutic alternative against MM.

L57 ANSWER 24 OF 59 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2006346704 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16550602
TITLE: The histone deacetylase inhibitor, suberoylanilide hydroxamic acid, overcomes resistance of human breast cancer cells to Apo2L /TRAIL.
AUTHOR: Butler Lisa M; Liapis Vasilios; Bouralexis Stelios; Welldon Katie; Hay Shelley; Thai Le M; Labrinidis Agatha; Tilley Wayne D; Findlay David M; Evdokiou Andreas
CORPORATE SOURCE: Dame Roma Mitchell Cancer Research Laboratories, University of Adelaide and Hanson Institute, Adelaide, SA, Australia.
SOURCE: International journal of cancer. Journal international du cancer, (2006 Aug 15) Vol. 119, No. 4, pp. 944-54. Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 9 Jun 2006
Last Updated on STN: 10 Aug 2006
Entered Medline: 9 Aug 2006

AB While the apoptosis-inducing ligand Apo2L/TRAIL is a promising new agent for the treatment of cancer, the sensitivity of cancer cells for induction of apoptosis by Apo2L/TRAIL varies considerably. Identification of agents that can be used in combination with Apo2L/TRAIL to enhance apoptosis in breast

cancer cells would increase the potential utility of this agent as a breast cancer therapeutic. Here, we show that the histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), can sensitize Apo2L/ TRAIL-resistant breast cancer cells to Apo2L/ TRAIL-induced apoptosis. Importantly, neither Apo2L /TRAIL alone, nor in combination with SAHA, affected the viability of normal human cells in culture. Apo2L /TRAIL-resistant MDA-MB-231 breast cancer cells, generated by long-term culture in the continuous presence of Apo2L/ TRAIL, were resensitized to Apo2L/TRAIL -induced apoptosis by SAHA. The sensitization of these cells by SAHA was accompanied by activation of caspase 8, caspase 9 and caspase 3 and was concomitant with Bid and PARP cleavage. The expression of the proapoptotic protein, Bax, increased significantly with SAHA treatment and high levels of Bax were maintained in the combined treatment with Apo2L/ TRAIL. Treatment with SAHA increased cell surface expression of DR5 but not DR4. Interestingly, SAHA treatment also resulted in a significant increase in cell surface expression of DcR1. Taken together, our findings indicate that the use of these 2 agents in combination may be effective for the treatment of breast cancer.
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L57 ANSWER 25 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2007:268199 BIOSIS Full-text
DOCUMENT NUMBER: PREV200700259556
TITLE: The novel histone deacetylase inhibitor OSU-HDAC42 has class I and II histone deacetylase (HDAC) inhibitory activity and represents a novel therapy for chronic lymphocytic leukemia.
AUTHOR(S): West, Derek A. [Reprint Author]; Lucas, David M.; Davis, Melanie E.; De lay, Michael D.; Johnson, Amy J.; Guster, Sara E.; Freitas, Michael A.; Parthun, Mark R.; Wang, Dasheng; Kulp, Samuel K.; Grever, Michael R.; Chen, Ching-Shih; Byrd, John C.
CORPORATE SOURCE: Ohio State Univ, Coll Pharm, Columbus, OH 43210 USA
SOURCE: Blood, (NOV 16 2006) Vol. 108, No. 11, Part 1, pp. 794A-795A.
Meeting Info.: 48th Annual Meeting of the American-Society-of-Hematology. Orlando, FL, USA. December 09 -12, 2006. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Apr 2007
Last Updated on STN: 25 Apr 2007

AB Inhibitors of histone deacetylase (HDAC) have generated major interest for the treatment of multiple cancers including B-cell Chronic Lymphocytic Leukemia (CLL). To date, HDAC inhibitors introduced for clinical development in CLL have been associated either with suboptimal activity relative to concentrations required to mediate cytotoxicity in vitro (Valproic Acid, MS-275, SAHA), or demonstrate unacceptable acute or long-term toxicities (depsipeptide) that limit their clinical potential. Fortunately, several alternative HDAC inhibitors are in pre-clinical or early clinical development. One such agent currently undergoing pre-clinical testing by the National Cancer Institute-sponsored RAID program is OSU-HDAC42 (s-HDAC-42), a novel, orally bioavailable phenylbutyrate-derived HDAC inhibitor with both in vitro and in vivo efficacy against prostate cancer cells. We therefore tested OSU-HDAC42 against CD19-positive cells obtained from patients with CLL to determine its potential in this disease. The LC, of OSU-HDAC42 in CLL cells

was 0.46 mu M at 48 hours of continuous incubation by MTT assay, which was corroborated by annexin V-FITC/propidium iodide flow cytometry. To determine the minimum amount of time that OSU-HDAC42 must be present to induce cell death, cells were incubated for various times, washed, resuspended in fresh media without drug, then assessed by MTT at a total of 48 hours incubation. The effects of OSU-HDAC42 were eliminated in CLL cells when drug was removed after 4 or 6 hours. However, there was a gradual increase in effect over time, and by 16 hours, approximately 60% of the cytotoxicity achieved with continuous incubation was retained. OSU-HDAC42 induced acetylation of histone proteins H3 and H4 as early as 4 hours that was dose and time dependent. LC/MS interrogation of OSU-HDAC42-treated CLL cells is currently underway to determine specific post-translational modification changes of all histone proteins and variants. OSU-HDAC42 also was able to sensitize CLL cells to TNF-Related Apoptosis Inducing Ligand (TRAIL) at 24 hours in a dose-dependent manner, supporting its class I HDAC inhibitory activity as recently reported by Inoue and colleagues (Cancer Res. 2006; 66:6785). Evidence of class 11 HDAC inhibitory activity was also observed with OSU-HDAC42 at 12 hours with acetylation of tubulin. Unlike depsipeptide, OSU-HDAC42 activated both caspase-8 and -9 followed by PARP processing. Cell death induced by OSU-HDAC42 was completely inhibited with pre-treatment by the pan-caspase inhibitor Z-VAD-FMK. In vivo experiments are underway to examine the efficacy of OSU-HDAC42 in several murine models of leukemia to confirm in vivo efficacy as well as influence on marine effector cells. Our data strongly support continued investigation of OSU-HDAC42 in CLL and related B-cell malignancies. (This work is supported by the,Leukemia & Lymphoma Society and the D. Warren Brown Foundation.)

L57 ANSWER 26 OF 59 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2006078812 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16465382
TITLE: Histone deacetylase inhibitors induce cell death and enhance the susceptibility to ionizing radiation, etoposide, and TRAIL in medulloblastoma cells.
AUTHOR: Sonnemann Jurgen; Kumar K Saravana; Heesch Sandra; Muller Cornelia; Hartwig Christoph; Maass Manfred; Bader Peter; Beck James F
CORPORATE SOURCE: Peter Holtz Research Center of Pharmacology and Experimental Therapeutics, Ernst Moritz Arndt University, Greifswald, Germany.
SOURCE: International journal of oncology, (2006 Mar) Vol. 28, No. 3, pp. 755-66.
Journal code: 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 9 Feb 2006
Last Updated on STN: 29 Mar 2006
Entered Medline: 28 Mar 2006

AB Histone deacetylase inhibitors (HDIs) are a promising new class of antineoplastic agents with the ability to induce apoptosis and growth arrest of cancer cells. In addition, HDIs have been suggested to enhance the anticancer efficacy of other therapeutic regimens, such as ionizing radiation (IR) or chemotherapy. The objective of this study was to evaluate the activity of HDIs against medulloblastoma cells when applied either as single

agents or in combination with IR, cytostatics, or TRAIL. The HDIs, suberoyl anilide hydroxamic acid (SAHA), sodium butyrate, and trichostatin A, were examined for their effects on the medulloblastoma cell lines, DAOY and UW228-2. We found that treatment with HDIs induced the dissipation of mitochondrial membrane potential, activation of caspase-9 and -3 and, consequently, apoptotic cell death. Moreover, all three HDIs significantly enhanced the cytotoxic effects of IR in DAOY cells. Likewise, treatment with SAHA markedly augmented the cytotoxicity of etoposide, while it had no effect on vincristine-mediated cell death. HDIs also potently increased the killing efficiency of TRAIL. TRAIL -induced, but not SAHA-induced, cell killing could be prevented by the caspase-8 inhibitor, z-IEDT-fmk. We conclude that HDIs may be useful for the treatment of medulloblastoma as monotherapy and particularly when given in combination with IR, appropriate cytostatics, or TRAIL.

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ACCESSION NUMBER: 2006480099 EMBASE Full-text
TITLE: Targeting caspase 8 to reduce the formation of metastases in neuroblastoma.
AUTHOR: McKee, Amy E.; Thiele, Carol J., Dr. (correspondence)
CORPORATE SOURCE: National Cancer Institute, Cell and Molecular Biology Section, Paediatric Oncology Branch, 10 Center Drive, Bethesda, MD 20892, United States. mckeea@mail.nih.gov; ct47a@nih.gov
SOURCE: Expert Opinion on Therapeutic Targets, (Oct 2006) Vol. 10, No. 5, pp. 703-708.
Refs: 44
ISSN: 1472-8222 CODEN: EOTTAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Oct 2006
Last Updated on STN: 24 Oct 2006

AB The clinical challenge in neuroblastoma is the presence of metastasis at diagnosis in the majority of patients. Caspase 8 is an integral protein in death receptor -associated apoptosis, and loss of caspase 8 via the epigenetic phenomenon of methylation in neuroblastoma has led to increased resistance to chemotherapy. Recent evidence suggests that caspase 8 loss may also contribute to a metastatic phenotype; thus, caspase 8 may prove to be an attractive target for therapy both in treating primary tumours as well as preventing and treating metastatic lesions. Numerous methods have been described to manipulate caspase 8 levels both in vitro and in vivo, and investigation into caspase 8 isoforms may also bring forth additional therapeutic targets. .COPYRGT. 2006 Informa UK Ltd.

L57 ANSWER 28 OF 59 MEDLINE on STN

ACCESSION NUMBER: 2006401391 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16820090
TITLE: Valproic acid, an antiepileptic drug with histone deacetylase inhibitory

activity, potentiates the cytotoxic effect of Apo2L/TRAIL on cultured thoracic cancer cells through mitochondria-dependent caspase activation.

AUTHOR: Ziauddin M Firdos; Yeow Wen-Shuz; Maxhimer Justin B; Baras Aris; Chua Alex; Reddy Rishindra M; Tsai Wilson; Cole George W Jr; Schrump David S; Nguyen Dao M

CORPORATE SOURCE: Section of Thoracic Oncology, Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.

SOURCE: Neoplasia (New York, N.Y.), (2006 Jun) Vol. 8, No. 6, pp. 446-57.
Journal code: 100886622. E-ISSN: 1476-5586.

PUB. COUNTRY: Canada

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., INTRAMURAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200608

ENTRY DATE: Entered STN: 6 Jul 2006
Last Updated on STN: 23 Aug 2006
Entered Medline: 22 Aug 2006

AB Inhibitors of histone deacetylases have been shown to enhance the sensitivity of cancer cells to tumor necrosis factor-related apoptosis-inducing ligand TRAIL-mediated cytotoxicity. Valproic acid (VA), a commonly used antiepileptic agent whose pharmacokinetics and toxicity profiles are well described, is a histone deacetylase inhibitor. This project aims to evaluate if VA can potentiate Apo2L/TRAIL-mediated cytotoxicity in cultured thoracic cancer cells and to elucidate the underlying molecular mechanism responsible for this effect. VA sensitized cultured thoracic cancer cells to Apo2L/TRAIL, as indicated by a 4-fold to a >20-fold reduction of Apo2L/ TRAIL IC50 values in combination-treated cells. Although VA (0.5-5 mM) or Apo2L/TRAIL (20 ng/ml) induced less than 20% cell death, VA + Apo2L/TRAIL combinations caused 60% to 90% apoptosis of cancer cells. Moreover, substantial activation of caspases 8, 9, and 3, which was observed only in cells treated with the drug combination, was completely suppressed by Bcl2 overexpression or by the caspase 9 inhibitor. Both the caspase 9 inhibitor and Bcl2 completely abrogated the substantial cytotoxicity and apoptosis induced by this combination, thus highlighting the pivotal role of the type II pathway in this process. These findings provide a rationale for the development of VA and Apo2L/TRAIL combination as a novel molecular therapeutic for thoracic cancers.

L57 ANSWER 29 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN DUPLICATE 10

ACCESSION NUMBER: 2006:354199 BIOSIS Full-text

DOCUMENT NUMBER: PREV200600356312

TITLE: HDAC inhibitor treatment of hepatoma cells induces both TRAIL-independent apoptosis and restoration of sensitivity to TRAIL.

AUTHOR(S): Pathil, Anita; Armeanu, Sorin; Venturelli, Sascha; Mascagni, Paolo; Weiss, Thomas S.; Gregor, Michael; Lauer, Ulrich M.; Bitzer, Michael [Reprint Author]

CORPORATE SOURCE: Med Univ Clin, Dept Internal Med 1, Otfried Muller Str 10, D-72076 Tubingen, Germany
michael.bitzer@uni-tuebingen.de

SOURCE: Hepatology, (MAR 2006) Vol. 43, No. 3, pp. 425-434.
CODEN: HPTLD9. ISSN: 0270-9139.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 19 Jul 2006
Last Updated on STN: 19 Jul 2006

AB Hepatocellular carcinoma (HCC) displays a striking resistance to chemotherapeutic drugs or innovative tumor cell apoptosis-inducing agents such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Recently, we found 2 histone deacetylase inhibitors (HDAC-I), valproic acid and ITF2357, exhibiting inherent therapeutic activity against HCC. In TRAIL-sensitive cancer cells, the mechanism of HDAC-I-induced cell death has been identified to be TRAIL-dependent by inducing apoptosis in an autocrine fashion. In contrast, in HCC-derived cells' a prototype of TRAIL-resistant tumor cells, we found a HDAC -I-mediated apoptosis that works independently of TRAIL and upregulation of death receptors or their cognate ligands. Interestingly, TRAIL resistance could be overcome by a combinatorial application of HDAC-I and TRAIL , increasing the fraction of apoptotic cells two- to threefold compared with HDAC-I treatment alone, whereas any premature HDAC-I withdrawal rapidly restored TRAIL resistance. Furthermore, a tumor cell-specific down-regulation of the FLICE inhibitory protein (FLIP) was observed, constituting a new mechanism of TRAIL sensitivity restoration by HDAC-I. In contrast, FLIP levels in primary human hepatocytes (PHH) from different donors were upregulated by HDAC-I. Importantly, combination HDAC-I/ TRAIL treatment did not induce any cytotoxicity in nonmalignant PHH. In conclusion, HDAC-I compounds, exhibiting a favorable in vivo profile and inherent activity against HCC cells, are able to selectively overcome the resistance of HCC cells toward TRAIL. Specific upregulation of intracellular FLIP protein levels in nonmalignant hepatocytes could enhance the therapeutic window for clinical applications of TRAIL, opening up a highly specific new treatment option for advanced HCC.

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ACCESSION NUMBER: 2007:245121 BIOSIS Full-text
DOCUMENT NUMBER: PREV200700246224
TITLE: OSU-HDAC42, a novel histone deacetylase inhibitor, induces apoptosis in a caspase-dependent manner and induces p(21WAF1/CIP1) and p16 expression in multiple myeloma cell lines.
AUTHOR(S): White, Valerie L. [Reprint Author]; Zhang, Shuhong; Lucas, David; Chen, Ching-Shih; Farag, Sherif S.
CORPORATE SOURCE: Ohio State Univ, Ctr Comprehens Canc, Columbus, OH 43210 USA
SOURCE: Blood, (NOV 16 2006) Vol. 108, No. 11, Part 2, pp. 359B.
Meeting Info.: 48th Annual Meeting of the American-Society-of-Hematology. Orlando, FL, USA. December 09 -12, 2006. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Apr 2007
Last Updated on STN: 30 Jan 2008

AB Multiple myeloma (MM) is a neoplastic disorder characterized by accumulation of slowly-proliferating clonal plasma cells. OSU-HDAC42 [a.k.a. (S)-HDAC-42] is a novel histone deacetylase inhibitor that induces apoptosis in various types of cancer cells and is being developed as an anti- cancer therapy in the NCI Rapid Access to Intervention Therapy (RAID) program. In this study, we tested the in vitro activity of OSU-HDAC42 against human MM cells. OSU-HDAC42 induced myeloma cell death, with an LC50 of less than 1.6 mu M after 48 hours in the four cell lines tested - U266, IM-9, RPMI 8226 and ARH-77 using the MTT

assay. OSU-HDAC42 induced cleavage of caspases 3, 8 and 9, as well as polyADP-ribose polymerase (PARP). Addition of the pan-caspase inhibitor Q-VD-OPH before exposure to the drug prevented apoptosis at 48 hours, as determined by Annexin V/propidium, iodide staining. These results indicate that OSU-HDAC42 induced apoptosis by a mainly caspase-dependent manner. Bax expression was up-regulated at 24 and 48 hours, while Bcl-2 remains relatively constant. Mcl-1 showed increasing cleavage at increasing doses of OSU-HDAC42. These findings support a mitochondrial pathway of apoptosis. Cell cycle suppressor proteins p21WAF1/CIP1 and p16 were also significantly induced after treatment with the drug, suggesting that OSU-HDAC42 may also acts on pathways to halt cell cycle progression. In addition, the gp130 (signal-transducing) subunit of the IL-6 receptor was downregulated by OSU-HDAC42 exposure. The tyrosine-phosphorylated form of STAT3, which is phosphorylated by dimerized gp 130, was also dramatically reduced following incubation with OSU-HDAC42, supporting the finding that gp 130 expression is diminished. As IL-6 is an important growth and survival factor for MM cells, down-regulation of gp130 may be an important mechanism for the activity of OSU-HDAC42 against MM cells. TRAIL, FasL, XIAP, and p53 expression were not affected by OSU-HDAC42. While other HDAC inhibitors have been shown to activate the death receptor pathway or down-regulate XIAP, this was not observed with OSU-HDAC42 in myeloma cells. In conclusion, OSU-HDAC42 has in vitro activity against myeloma cells and acts via activation of caspases, inducing the cell cycle suppressors p21(WAF1/CIP1) and p16, as well as interfering with the IL-6 signal transduction pathway.

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ACCESSION NUMBER: 2006086266 EMBASE Full-text
TITLE: In vitro efficacy of AdTRAIL gene therapy of bladder cancer is enhanced by trichostatin A-mediated restoration of CAR expression and downregulation of cFLIP and Bcl-X(L).
AUTHOR: El-Zawahry, A.; Lu, P.; White, S.J.; Voelkel-Johnson, C., Dr. (correspondence)
CORPORATE SOURCE: Department of Microbiology and Immunology, Medical University of South Carolina, Charleston, SC, United States. johnsocv@musc.edu
AUTHOR: Voelkel-Johnson, C., Dr. (correspondence)
CORPORATE SOURCE: Department of Microbiology and Immunology, Medical University of SC, 173 Ashley Ave, Charleston, SC 29403, United States. johnsocv@musc.edu
SOURCE: Cancer Gene Therapy, (Mar 2006) Vol. 13, No. 3, pp. 281-289.
Refs: 39
ISSN: 0929-1903 E-ISSN: 1476-5500 CODEN: CGTHEG
PUBLISHER IDENT.: 7700905
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
028 Urology and Nephrology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 2006
Last Updated on STN: 1 Feb 2007

AB Current therapies for bladder cancer are suboptimal and adenoviral gene therapy has been explored as an alternative treatment. In this study, we evaluated the in vitro efficacy of an adenovirus expressing TNF-related

apoptosis-inducing ligand (AdTRAIL). At low concentrations of virus, T24 cells were more resistant to AdTRAIL-induced apoptosis than 5637 bladder carcinoma cells. Resistance in T24 cells correlated with poor infectivity and lack of surface expression of coxsackie and adenovirus receptor (CAR). Pretreatment with low concentrations of the histone deacetylase inhibitor trichostatin A, restored CAR expression in T24 cells, which facilitated viral infection and resulted in apoptosis at low concentrations of AdTRAIL. In addition, trichostatin A reduced the expression of Bcl-X(L) and cFLIP resulting in increased sensitivity to recombinant TRAIL . Overexpression of cFLIP inhibited TRAIL-mediated killing in trichostatin A pretreated cells, indicating that downregulation of this antiapoptotic protein is required for sensitization. Therefore, trichostatin A can enhance the efficacy of AdTRAIL by restoring CAR expression and by generating a more pro-apoptotic phenotype that would facilitate bystander activity of TRAIL. Combination of histone deacetylase inhibitors with intravesical AdTRAIL gene therapy may be a novel treatment strategy for bladder cancer. .COPYRGT. 2006 Nature Publishing Group All rights reserved.

L57 ANSWER 32 OF 59 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2005646593 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16328060
TITLE: Histone deacetylase inhibition by valproic acid down-regulates c-FLIP/CASH and sensitizes hepatoma cells towards CD95- and TRAIL receptor-mediated apoptosis and chemotherapy.
AUTHOR: Schuchmann M; Schulze-Bergkamen H; Fleischer B; Schattenberg J M; Siebler J; Weinmann A; Teufel A; Worns M; Fischer T; Strand S; Lohse A W; Galle P R
CORPORATE SOURCE: First Department of Medicine, Johnnes Gutenberg University of Mainz, Germany.. schuchm@mail.uni-mainz.de
SOURCE: Oncology reports, (2006 Jan) Vol. 15, No. 1, pp. 227-30.
Journal code: 9422756. ISSN: 1021-335X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 6 Dec 2005
Last Updated on STN: 11 Mar 2006
Entered Medline: 10 Mar 2006

AB Hepatocellular carcinoma (HCC) is highly resistant to chemotherapy, leading to a poor prognosis of advanced disease. Inhibitors of histone deacetylase (HDACi) induce re-differentiation in tumor cells and thereby re-establish sensitivity towards apoptotic stimuli. HDACi are entering the clinical stage of tumor treatment, and several substances are currently being tested in clinical trials to prove their efficacy in the treatment of leukemias and solid tumors. In this study, we investigated the impact of the HDACi valproic acid (VA) on TRAIL- and CD95-mediated apoptosis in hepatoma cells, as well as its sensitizing effect on a chemotherapeutic agent. Treatment of HepG2 cells with VA increased sensitivity to CD95-mediated apoptosis (4% apoptosis vs. 42%), and treatment with epirubicin (74% vs. 90% viability). Caspase-3 activity was significantly enhanced in cells treated with VA plus anti-CD95 antibodies compared to cells treated with antibodies alone. In parallel, VA strongly augmented the effect of TNF-related apoptosis-inducing ligand (TRAIL or Apo2 ligand) on HepG2 cells (10% vs. 58% apoptosis). VA induced down-regulation of cellular FLICE-

inhibitory protein (c-FLIP/CASH, also known as Casper/iFLICE/FLAME-1/CLARP/MRIT/usurpin), providing a possible molecular mechanism underlying the increased sensitivity towards cell death-mediated apoptosis. HDAC inhibitors are a promising class for the treatment of leukemias. In addition, among other class members, VA deserves further evaluation as a treatment option for patients with advanced HCC.

L57 ANSWER 33 OF 59 MEDLINE on STN
ACCESSION NUMBER: 2006552966 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16930472
TITLE: Histone deacetylase inhibitors strongly sensitise neuroblastoma cells to TRAIL -induced apoptosis by a caspases-dependent increase of the pro- to anti-apoptotic proteins ratio.
AUTHOR: Muhlethaler-Mottet Annick; Flahaut Marjorie; Bourloud Katia Balmas; Auderset Katya; Meier Roland; Joseph Jean-Marc; Gross Nicole
CORPORATE SOURCE: Paediatric Oncology Research, Paediatric Department, University Hospital CHUV, CH-1011 Lausanne, Switzerland.. Annick.Muhlethaler@chuv.ch
SOURCE: BMC cancer, (2006) Vol. 6, pp. 214. Electronic Publication: 2006-08-24.
Journal code: 100967800. E-ISSN: 1471-2407.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 19 Sep 2006
Last Updated on STN: 4 Nov 2006
Entered Medline: 3 Nov 2006

AB BACKGROUND: Neuroblastoma (NB) is the second most common solid childhood tumour, an aggressive disease for which new therapeutic strategies are strongly needed. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis in most tumour cells, but not in normal tissues and therefore represents a valuable candidate in apoptosis-inducing therapies. Caspase -8 is silenced in a subset of highly malignant NB cells, which results in full TRAIL resistance. In addition, despite constitutive caspase-8 expression, or its possible restoration by different strategies, NB cells remain weakly sensitive to TRAIL indicating a need to develop strategies to sensitise NB cells to TRAIL. Histone deacetylase inhibitors (HDACIs) are a new class of anti-cancer agent inducing apoptosis or cell cycle arrest in tumour cells with very low toxicity toward normal cells. Although HDACIs were recently shown to increase death induced by TRAIL in weakly TRAIL-sensitive tumour cells, the precise involved sensitisation mechanisms have not been fully identified. METHODS: NB cell lines were treated with various doses of HDACIs and TRAIL , then cytotoxicity was analysed by MTS/PMS proliferation assays, apoptosis was measured by the Propidium staining method, caspases activity by colorimetric protease assays, and (in)activation of apoptotic proteins by immunoblotting. RESULTS: Sub-toxic doses of HDACIs strongly sensitised caspase-8 positive NB cell lines to TRAIL induced apoptosis in a caspases dependent manner. Combined treatments increased the activation of caspases and Bid, and the inactivation of the anti-apoptotic proteins XIAP, Bcl-x, RIP, and survivin, thereby increasing the pro- to anti-apoptotic protein ratio. It also enhanced the activation of the mitochondrial pathway. Interestingly, the kinetics of caspases activation and inactivation of anti-apoptotic proteins is accelerated by combined treatment with TRAIL and HDACIs compared to TRAIL alone. In contrast, cell surface expression of TRAIL-

receptors or TRAIL is not affected by sub-toxic doses of HDACIs. CONCLUSION: HDACIs were shown to activate the mitochondrial pathway and to sensitise NB cells to TRAIL by enhancing the amplitude of the apoptotic cascade and by restoring an apoptosis-prone ratio of pro- to anti-apoptotic proteins. Combining HDACIs and TRAIL could therefore represent a weakly toxic and promising strategy to target TRAIL -resistant tumours such as neuroblastomas.

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ACCESSION NUMBER: 2006:584145 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600594771
TITLE: Apoptosis-resistant human melanoma cells selected by prolonged exposure to TRAIL are more sensitive to necrotic cell death induced by cisplatin.
AUTHOR(S): Zhang, Xu Dong [Reprint Author]; Gillespie, Susan; Wu, Jing Jing; Borrow, Jodie; Hersey, Peter
CORPORATE SOURCE: Newcastle Mater Hosp, Inst Canc, Newcastle, NSW, Australia
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2006) Vol. 47, pp. 182-183.
Meeting Info.: 97th Annual Meeting of the American-Association-for-Cancer-Research (AACR). Washington, DC, USA. April 01 -05, 2006. Amer Assoc Canc Res.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Nov 2006
Last Updated on STN: 8 Nov 2006

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ACCESSION NUMBER: 2006463988 EMBASE Full-text
TITLE: Histone deacetylase inhibitors strongly sensitise neuroblastoma cells to TRAIL -induced apoptosis by a caspases-dependent increase of the pro- to anti-apoptotic proteins ratio.
AUTHOR: Muhlethaler-Mottet, Annick; Flahaut, Marjorie; Bourloud, Katia Balmas; Auderset, Katya; Meier, Roland; Gross, Nicole (correspondence)
CORPORATE SOURCE: Paediatric Oncology Research, Paediatric Department, University Hospital CHUV, CH-1011 Lausanne, Switzerland. Annick.Muhlethaler@chuv.ch; Katia.Balmas-Bourloud@chuv.ch; Nicole.Gross@chuv.ch; Roland.Meier@chuv.ch; Marjorie.Flahaut@chuv.ch; Katya.Auderset@chuv.ch
AUTHOR: Joseph, Jean-Marc
CORPORATE SOURCE: Paediatric Surgery, Paediatric Department, University Hospital CHUV, CH-1011 Lausanne, Switzerland. Jean-Marc.Joseph@chuv.ch
SOURCE: BMC Cancer, (24 Aug 2006) Vol. 6. arn. 214.
Refs: 41
ISSN: 1471-2407 E-ISSN: 1471-2407 CODEN: BCMACL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer

029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
008 Neurology and Neurosurgery

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Oct 2006
Last Updated on STN: 24 Oct 2006

AB Background: Neuroblastoma (NB) is the second most common solid childhood tumour, an aggressive disease for which new therapeutic strategies are strongly needed. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis in most tumour cells, but not in normal tissues and therefore represents a valuable candidate in apoptosis-inducing therapies. Caspase -8 is silenced in a subset of highly malignant NB cells, which results in full TRAIL resistance. In addition, despite constitutive caspase-8 expression, or its possible restoration by different strategies, NB cells remain weakly sensitive to TRAIL indicating a need to develop strategies to sensitise NB cells to TRAIL. Histone deacetylase inhibitors (HDACIs) are a new class of anti-cancer agent inducing apoptosis or cell cycle arrest in tumour cells with very low toxicity toward normal cells. Although HDACIs were recently shown to increase death induced by TRAIL in weakly TRAIL-sensitive tumour cells, the precise involved sensitisation mechanisms have not been fully identified. Methods: NB cell lines were treated with various doses of HDACIs and TRAIL , then cytotoxicity was analysed by MTS/PMS proliferation assays, apoptosis was measured by the Propidium staining method, caspases activity by colorimetric protease assays, and (in)activation of apoptotic proteins by immunoblotting. Results: Sub-toxic doses of HDACIs strongly sensitised caspase-8 positive NB cell lines to TRAIL induced apoptosis in a caspases dependent manner. Combined treatments increased the activation of caspases and Bid, and the inactivation of the anti-apoptotic proteins XIAP, Bcl-x, RIP, and survivin, thereby increasing the pro- to anti-apoptotic protein ratio. It also enhanced the activation of the mitochondrial pathway. Interestingly, the kinetics of caspases activation and inactivation of anti-apoptotic proteins is accelerated by combined treatment with TRAIL and HDACIs compared to TRAIL alone. In contrast, cell surface expression of TRAIL-receptors or TRAIL is not affected by sub-toxic doses of HDACIs. Conclusion: HDACIs were shown to activate the mitochondrial pathway and to sensitise NB cells to TRAIL by enhancing the amplitude of the apoptotic cascade and by restoring an apoptosis-prone ratio of pro- to anti-apoptotic proteins. Combining HDACIs and TRAIL could therefore represent a weakly toxic and promising strategy to target TRAIL -resistant tumours such as neuroblastomas. .COPYRGT. 2006 Muhlethaler-Motter et al; licensee Biomed Central Ltd.

L57 ANSWER 36 OF 59 WPIX COPYRIGHT 2008 THOMSON REUTERS on STN
ACCESSION NUMBER: 2005-233428 [24] WPIX
DOC. NO. CPI: C2005-074096 [24]
TITLE: Combination useful for treating or preventing e.g. premalignant proliferative disease comprises death receptor ligand, and histone deacetylase inhibitor
DERWENT CLASS: B05
INVENTOR: ATADJA P W; BHALLA K N; ATADJA P; BHALLA K
PATENT ASSIGNEE: (NOVS-C) NOVARTIS AG; (NOVS-C) NOVARTIS PHARMA GMBH; (UYSF-N) UNIV SOUTH FLORIDA; (ATAD-I) ATADJA P W; (BHAL-I) BHALLA K N
COUNTRY COUNT: 107

PATENT INFO ABBR.:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2005025619	A1	20050324	(200524)*	EN	39[0]	
EP 1667720	A1	20060614	(200641)	EN		
AU 2004271730	A1	20050324	(200670)	EN		
BR 2004014506	A	20061107	(200674)	PT		
CN 1852737	A	20061025	(200715)	ZH		
JP 2007505860	W	20070315	(200722)	JA	32	
MX 2006003127	A1	20061101	(200737)	ES		
IN 2006CN00926	P4	20070615	(200765)	EN		
US 20070258972	A1	20071108	(200774)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005025619	A1	WO 2004-EP10468	20040917
AU 2004271730	A1	AU 2004-271730	20040917
BR 2004014506	A	BR 2004-14506	20040917
CN 1852737	A	CN 2004-80026541	20040917
EP 1667720	A1	EP 2004-765360	20040917
EP 1667720	A1	WO 2004-EP10468	20040917
BR 2004014506	A	WO 2004-EP10468	20040917
JP 2007505860	W	WO 2004-EP10468	20040917
MX 2006003127	A1	WO 2004-EP10468	20040917
IN 2006CN00926	P4	WO 2004-EP10468	20040917
JP 2007505860	W	JP 2006-526597	20040917
IN 2006CN00926	P4	IN 2006-CN926	20060316
MX 2006003127	A1	MX 2006-3127	20060317
US 20070258972	A1 Provisional	US 2003-504655P	20030918
US 20070258972	A1	WO 2004-EP10468	20040917
US 20070258972	A1	US 2007-571734	20070319

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
EP 1667720	A1	Based on	WO 2005025619	A
AU 2004271730	A1	Based on	WO 2005025619	A
BR 2004014506	A	Based on	WO 2005025619	A
JP 2007505860	W	Based on	WO 2005025619	A
MX 2006003127	A1	Based on	WO 2005025619	A

PRIORITY APPLN. INFO: US 2003-504655P 20030918
US 2007-571734 20070319

AN 2005-233428 [24] WPIX

AB WO 2005025619 A1 UPAB: 20060122

NOVELTY - A combination comprises death receptor ligand, and a histone deacetylase inhibitor (HDAI).

ACTIVITY - Cytostatic; Antiangiogenic; Antipsoriatic; Antiarteriosclerotic; Vasotropic.

Primary AML cells were treated with LAQ824 (100 nM) alone, Apo-2/L TRAIL (100 ng/ml) alone and combination of LAQ824 and Apo-2/L TRAIL for 24 hours and showed % apoptosis as 14.5, 7.6 and 27.2, respectively.

MECHANISM OF ACTION - None given.

USE - For treating or preventing premalignant proliferative disease e.g. leukemia in mammal (preferably human) (claimed), for treating tumor, hypreplasias, fibrosis, angiogenesis, psoriasis, atherosclerosis, smooth muscle proliferation, stenosis, restenosis following angioplasty.

ADVANTAGE - The HDAI enhances death receptor ligand. The synergistic combination is efficacious and safe. Also, the components of the combination can be administered in lower dosage.

L57 ANSWER 37 OF 59 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2005255944 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15897598
TITLE: Novel histone deacetylase inhibitors in the treatment of thyroid cancer.
AUTHOR: Mitsiades Constantine S; Poulaki Vassiliki; McMullan Ciaran; Negri Joseph; Fanourakis Galinos; Goudopoulou Athina; Richon Victoria M; Marks Paul A; Mitsiades Nicholas
CORPORATE SOURCE: Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA.. cmitsiades@partners.org
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2005 May 15) Vol. 11, No. 10, pp. 3958-65.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 18 May 2005
Last Updated on STN: 24 Aug 2005
Entered Medline: 23 Aug 2005

AB Histone deacetylases (HDAC) and histone acetyltransferases exert opposing enzymatic activities that modulate the degree of acetylation of histones and other intracellular molecular targets, thereby regulating gene expression, cellular differentiation, and survival. HDAC inhibition results in accumulation of acetylated histones and induces differentiation and/or apoptosis in transformed cells. In this study, we characterized the effect of two HDAC inhibitors, suberoylanilide hydroxamic acid (SAHA) and m-carboxycinnamic acid bis-hydroxamide, on thyroid carcinoma cell lines, including lines originating from anaplastic and medullary carcinomas. In these models, both SAHA and m-carboxycinnamic acid bis-hydroxamide induced growth arrest and caspase-mediated apoptosis and increased p21 protein levels, retinoblastoma hypophosphorylation, BH3-interacting domain death agonist cleavage, Bax up-regulation, down-regulation of Bcl-2, A1, and Bcl-x(L) expression, and cleavage of poly(ADP-ribose) polymerase and caspase-8, -9, -3, -7, and -2. Transfection of Bcl-2 cDNA partially suppressed SAHA-induced cell death. SAHA down-regulated the expression of the apoptosis inhibitors FLIP and cIAP-2 and sensitized tumor cells to cytotoxic chemotherapy and death receptor activation. Our studies provide insight into the tumor type-specific mechanisms of antitumor effects of HDAC inhibitors and a framework for future clinical applications of HDAC inhibitors in patients with thyroid cancer, including histologic subtypes (e.g., anaplastic and medullary thyroid carcinomas) for which limited, if any, therapeutic options are available.

L57 ANSWER 38 OF 59 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 2005593017 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16273296
TITLE: Interactive effects of histone deacetylase inhibitors and TRAIL on apoptosis in human leukemia cells: involvement of both death receptor

and mitochondrial pathways.
AUTHOR: Shankar Sharmila; Singh Thiyam R; Fandy Tamer E; Luetrakul Thitidaj; Ross Douglas D; Srivastava Rakesh K
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Molecular and Cellular Biology Program, University of Maryland, Baltimore, MD 21201-1180, USA.
SOURCE: International journal of molecular medicine, (2005 Dec) Vol. 16, No. 6, pp. 1125-38.
Journal code: 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200602
ENTRY DATE: Entered STN: 8 Nov 2005
Last Updated on STN: 22 Feb 2006
Entered Medline: 21 Feb 2006

AB In the present study, we aimed to elucidate the mechanism responsible for the interactive effects of histone deacetylase (HDAC) inhibitors [suberoylanilide hydroxamic acid (SAHA), MS-275, m-carboxycinnamic acid bishydroxamide (CBHA), and trichostatin-A (TSA)] and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) on apoptosis in leukemia cells. HDAC inhibitors enhance the apoptosis-inducing potential of TRAIL in leukemia cells (HL60, Jurkat, K562, and U937) through multiple mechanisms; up-regulation of DR4, DR5, Bak, Bax, Bim, Noxa and PUMA, down-regulation of IAPs, Mcl-1, Bcl-2, Bcl-XL and cFLIP, release of mitochondrial proteins (cytochrome c, Smac/DIABLO and Omi/Htr2) to the cytosol, induction of p21WAF1/CIP1 and p27KIP1, activation of caspase-3 and cleavage of poly(ADP-ribose) polymerase (PARP). The sequential treatment of cells with HDAC inhibitors followed by TRAIL was more effective in inducing apoptosis than the concurrent treatment or single agent alone. The up-regulation of death receptors and inhibition of cFLIP by HDAC inhibitors will increase the ability of TRAIL to induce apoptosis, due to enhance activation of caspase-8, cleavage of Bid, and release of mitochondrial proteins to the cytosol, and subsequent activation of caspase-9 and caspase-3. Thus, the combination of HDAC inhibitors and TRAIL can be used as a new therapeutic approach for the treatment of leukemia.

L57 ANSWER 39 OF 59 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005492048 EMBASE Full-text
TITLE: Apoptosis-based therapies for hematological malignancies.
AUTHOR: Petronelli, Alessia; Riccioni, Roberta; Pasquini, Luca; Petrucci, Eleonora; Testa, Ugo (correspondence)
CORPORATE SOURCE: Department of Hematology, Oncology and Molecular Medicine, Istituto Superiore di Sanita, Viale Regina Elena 299, 00161 Rome, Italy. u.testa@iss.it
SOURCE: Drugs of the Future, (Jul 2005) Vol. 30, No. 7, pp. 707-723.
Refs: 110
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
025 Hematology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Dec 2005
Last Updated on STN: 15 Dec 2005

AB Apoptosis, or programmed cell death, is central to the development and homeostasis of the hemopoietic system. Dysregulation of apoptosis plays an important role in the development of a variety of human pathologies, including cancer, autoimmune diseases and neurodegenerative disorders. Studies carried out in recent years have shown that leukemia, lymphoma and multiple myeloma cells invariably have abnormalities in one or more apoptotic pathways, determining a survival advantage of these cells over their normal counterparts. Furthermore, abnormalities in the apoptotic response also play a pivotal role in the development of drug resistance by leukemia/lymphoma cells. Tremendous progress in elucidating the structure and function of the core components of the apoptosis machinery have led to the identification of many molecular apoptotic targets for the development of new drugs targeting antiapoptotic molecules abnormally expressed or dysregulated in cancer cells. In this review, we describe some of the drug discovery targets thus far identified within the core apoptotic machinery, the corresponding drugs that have been developed, their effects on leukemia /lymphoma cells and their potential impact on the therapy of these diseases. Copyright .COPYRGT. 2005 Prous Science.

L57 ANSWER 40 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:259783 BIOSIS Full-text
DOCUMENT NUMBER: PREV200700269850
TITLE: Histone deacetylase inhibitors induce death receptor 5/ TRAIL-R2, and potentiate TRAIL -mediated apoptosis in human malignant tumor cells.
AUTHOR(S): Nakata, Susumu [Reprint Author]; Yoshida, Tatsushi; Horinaka, Mano; Shiraishi, Takumi; Wakada, Miki; Sakai, Toshiyuki
CORPORATE SOURCE: Kyoto Prefectural Univ Med, Kyoto, Japan
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2005) Vol. 46, pp. 413. Meeting Info.: 96th Annual Meeting of the American-Association-for-Cancer-Research. Anaheim, CA, USA. April 16 -20, 2005. Amer Assoc Canc Res. ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Apr 2007
Last Updated on STN: 11 Jul 2007

L57 ANSWER 41 OF 59 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2005110670 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15515013
TITLE: Involvement of the tumor necrosis factor (TNF)/TNF receptor system in leukemic cell apoptosis induced by histone deacetylase inhibitor depsipeptide (FK228).
AUTHOR: Sutheesophon Krittaya; Nishimura Noriko; Kobayashi Yukiko; Furukawa Yutaka; Kawano Mikihiko; Itoh Kouichi; Kano Yasuhiko; Ishii Hideshi; Furukawa Yusuke
CORPORATE SOURCE: Division of Stem Cell Regulation, Center for Molecular

Medicine, Jichi Medical School, 33311-1 Yakushiji, Minamikachi-machi, Tochigi 329-0498, Japan.
SOURCE: Journal of cellular physiology, (2005 May) Vol. 203, No. 2, pp. 387-97.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 3 Mar 2005
Last Updated on STN: 2 Jun 2005
Entered Medline: 1 Jun 2005

AB Inhibition of histone deacetylase (HDAC) is a novel strategy for the treatment of leukemias via restoration of aberrantly silenced genes. In this study, we conducted a detailed analysis of anti-leukemic effects of an HDAC inhibitor (HDI), depsipeptide (FK228), using myeloid leukemia cell lines HL-60 and K562. DNA chip analysis revealed upregulation of TNF-alpha mRNA and a number of molecules involved in TNF-signaling such as TRAF-6, caspases-10, and -7 in depsipeptide-treated HL-60 cells, which prompted us to examine the involvement of the TNF/TNF receptor system in the anti-leukemic effects of the drug. Upregulation of TNF-alpha was induced by depsipeptide in HL-60 and K562 cells, which expressed type I TNF receptors (TNF-RI). Depsipeptide activated caspases- 8 and -10, which in turn cleave caspases-3 and -7, leading to apoptotic cell death in both cell lines. Anti-TNF-alpha neutralizing antibody and short interfering RNA (siRNA) against TNF-RI alleviated the activation of the caspase cascade and the induction of apoptosis, indicating the presence of an autocrine loop. Finally, we demonstrated that the enhanced production of TNF-alpha by depsipeptide was due to transcriptional activation of the TNF-alpha gene through hyperacetylation of histones H3 and H4 in its promoter region (-208 to +35). These results suggest that autocrine production of TNF-alpha plays a role in the cytotoxicity of depsipeptide against a subset of leukemias.
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L57 ANSWER 42 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:181448 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600183560
TITLE: The histone deacetylase inhibitor SAHA induces caspase-dependent apoptosis in chronic lymphocytic leukemia cells.
AUTHOR(S): Lagneaux, Laurence [Reprint Author]; Meuleman, Nathalie; Delforge, Alain; Dejeneffe, Marielle; Massy, Martine; Mortier, Christine; Bron, Dominique
CORPORATE SOURCE: Inst Jules Bordet, B-1000 Brussels, Belgium
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 347A-348A.
Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006

AB BACKGROUND: Chronic lymphocytic leukemia (CLL) is a clinically heterogeneous disease characterized by the accumulation of CD5+ B cells with significant resistance to apoptosis and therefore prolonged survival. CLL remains an incurable disease requiring innovative new approaches to improve overall patient outcome.OBJECTIVE: Historic deacetylase inhibitors such as suberoylanilide hydroxamic acid (SAHA) have shown antitumoral activity at micromolar concentrations in a variety of human cancers in vitro and in vivo. These different studies suggested extrinsic, intrinsic and caspase-independent apoptosis as relevant death pathway depending upon cell types.RESULTS: In this study, we examined the effects of SAHA on CLL cells in vitro. SAHA induced apoptosis in a dose-dependent manner in all (n=25) CLL samples tested, including previously untreated and chemo-resistant CLL patients. The level of apoptosis, as measured by annexin binding to exposed PS residues, increased after 48 hours of SAHA treatment and was significant in the treated cells at concentrations of 10 and 20 PM (respectively 45 5 and 52 +/- 4% of apoptotic cells versus 29.5 +/- 4 for untreated cells, $p < 0.0001$). The pre-treatment of cells with the pan-caspase inhibitor Z-VAD before SAHA-treatment had no effect on PS externalization but inhibited DNA degradation demonstrating that caspases are critical for inducing DNA fragmentation. Using specific caspase inhibitors (DEVD, VEID and IETD) we demonstrated the participation of caspases-3, -6 and -8 in cell apoptosis. In addition, inhibition of the initiator caspase in the intrinsic/mitochondrial pathway, caspase-9, did not influence cell apoptosis. Thus, extrinsic pathway seems activated during SAHA-induced apoptosis. We have next investigated the expression of FAS and TRAIL-RI (DR4) by CLL cells after SAHA treatment. Only a small proportion of CLL cells displayed detectable expression of CD95 (12.5 +/- 2% CD19+CD95+). 24h treatment with SAHA resulted in increase in FAS expression compared to control (33 +/- 5.6%, $p < 0.02$). However, a FAS-blocking antibody (ZB4) did not inhibit SAHA-induced apoptosis arguing against a role of FAS/FAS-L signaling pathway in the induction of apoptosis by SAHA. The expression of TRAIL-R1 was very low and not upregulated by SAHA treatment. To explore the mechanism by which SAHA triggers the extrinsic pathway in CLL cells, the effects of SAHA on the level of various apoptosis-regulatory proteins (FLIP, FADD...) are now evaluated.CONCLUSIONS: SAHA induces apoptosis in CLL cells via the extrinsic pathway involving caspase-8 activation. Since the majority of cytotoxic agents operate via the intrinsic pathway and since defects in the mitochondrial pathway exist in chemoresistant CLL patients, it is important to identify agents that exert their cytotoxic effect via the extrinsic pathway. Moreover, the combination of SAHA with conventional drugs could be of therapeutic effect in CLL.

L57 ANSWER 43 OF 59 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 2005509440 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16109447
TITLE: Sodium butyrate sensitises human pancreatic cancer cells to both the intrinsic and the extrinsic apoptotic pathways.
AUTHOR: Natoni Federica; Diolordi Laura; Santoni Claudio; Gilardini Montani Maria Saveria
CORPORATE SOURCE: Department of Environmental Science, University of La Tuscia, Viterbo, Italy.
SOURCE: Biochimica et biophysica acta, (2005 Sep 30) Vol. 1745, No. 3, pp. 318-29.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 27 Sep 2005
Last Updated on STN: 14 Mar 2006
Entered Medline: 13 Mar 2006

AB Pancreatic cancer is characterised by a highly malignant phenotype with a marked resistance to conventional therapies and to apoptotic activators. Here, we demonstrate that sodium butyrate (NaBt), an inhibitor of histone deacetylases, sensitises human pancreatic cancer cell lines to both mitochondria- and Fas-mediated apoptosis. The analysis of anti-apoptotic and pro-apoptotic members of the Bcl-2 family in untreated pancreatic cancer cell lines shows a generalised low expression of Bcl-2 and a strong expression of Bcl-xL. NaBt treatment results in a marked down-regulation of Bcl-xL expression, mitochondrial membrane depolarization, cytochrome c release from mitochondria, activation of caspase-9 and -3 and apoptosis induction. Furthermore, NaBt sensitises pancreatic cancer cells to Fas-mediated apoptosis as well. In fact, the combined treatment with NaBt and the agonistic antibody anti-Fas (CH11) is able to induce apoptosis at an early time, in which neither NaBt nor CH11 alone induce apoptosis. Down-regulation of FLIP and activation of caspase-8 allow apoptosis to occur. These findings suggest that sodium butyrate could represent a good candidate for the development of new therapeutic strategies aimed at improving chemotherapy and immunotherapy in pancreatic cancer.

L57 ANSWER 44 OF 59 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 2004413578 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15208660
TITLE: Histone deacetylase inhibitors upregulate death receptor 5/ TRAIL-R2 and sensitize apoptosis induced by TRAIL/APO2-L in human malignant tumor cells.
AUTHOR: Nakata Susumu; Yoshida Tatsushi; Horinaka Mano; Shiraishi Takumi; Wakada Miki; Sakai Toshiyuki
CORPORATE SOURCE: Department of Molecular-Targeting Cancer Prevention, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramcahi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
SOURCE: Oncogene, (2004 Aug 19) Vol. 23, No. 37, pp. 6261-71. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20 Aug 2004
Last Updated on STN: 10 Sep 2004
Entered Medline: 9 Sep 2004

AB Death receptor 5 (DR5) is a receptor for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). TRAIL is a promising candidate for cancer therapeutics due to its ability to induce apoptosis selectively in cancer cells. Here, we report that histone deacetylase inhibitors (HDACIs) such as trichostatin A (TSA), sodium butyrate, and suberoylanilide hydroxamic acid (SAHA) upregulated DR5 expression in various human malignant tumor cells. An RNase protection assay demonstrated that HDACIs induced DR5 mRNA markedly but not that of other death receptor family members in Jurkat cells. HDACIs increased DR5 mRNA and protein in a dose- and time-dependent manner. We also show TSA increased DR5 promoter

activity using a luciferase promoter assay. Furthermore, we demonstrated that HDACIs strongly sensitized exogenous soluble recombinant human TRAIL-induced apoptosis synergistically in Jurkat and HL-60 cells that were tolerant to TRAIL alone. The combined use of HDACIs and TRAIL in suboptimal concentrations induced Bid cleavage and activation of caspase-8, -10, -3, and -9. Human recombinant DR5/Fc chimera protein, zVAD-fmk pancaspase inhibitor, and caspase-8 and -10 inhibitors efficiently reduced apoptosis induced by cotreatment with HDACIs and TRAIL. Furthermore, TSA did not significantly induce DR5 protein and HDACIs did not enhance TRAIL -induced apoptosis in normal human peripheral blood mononuclear cells. These results suggest that this combined treatment with HDACIs and TRAIL is a promising strategy for new cancer therapeutics.

L57 ANSWER 45 OF 59 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 2004165911 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15059915
TITLE: Cotreatment with histone deacetylase inhibitor LAQ824 enhances Apo-2L/ tumor necrosis factor-related apoptosis inducing ligand-induced death inducing signaling complex activity and apoptosis of human acute leukemia cells.
AUTHOR: Guo Fei; Sigua Celia; Tao Jianguo; Bali Purva; George Prince; Li Yunqing; Wittmann Sylvie; Moscinski Lynn; Atadja Peter; Bhalla Kapil
CORPORATE SOURCE: Department of Interdisciplinary Oncology, Moffitt Cancer Center and Research Institute University of South Florida, Tampa, Florida 33612, USA.
SOURCE: Cancer research, (2004 Apr 1) Vol. 64, No. 7, pp. 2580-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 3 Apr 2004
Last Updated on STN: 20 May 2004
Entered Medline: 19 May 2004

AB Present studies demonstrate that treatment with the histone deacetylases inhibitor LAQ824, a cinnamic acid hydroxamate, increased the acetylation of histones H3 and H4, as well as induced p21(WAF1) in the human T-cell acute leukemia Jurkat, B lymphoblast SKW 6.4, and acute myelogenous leukemia HL-60 cells. This was associated with increased accumulation of the cells in the G(1) phase of the cell cycle, as well as accompanied by the processing and activity of caspase-9 and -3, and apoptosis. Exposure to LAQ824 increased the mRNA and protein expressions of the death receptors DR5 and/or DR4, but reduced the mRNA and protein levels of cellular FLICE-inhibitory protein (c-FLIP). As compared with treatment with Apo-2L/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or LAQ824 alone, pretreatment with LAQ824 increased the assembly of Fas-associated death domain and caspase- 8, but not of c-FLIP, into the Apo-2L/ TRAIL-induced death-inducing signaling complex. This increased the processing of caspase-8 and Bcl-2 interacting domain (BID), augmented cytosolic accumulation of the prodeath molecules cytochrome-c, Smac and Omi, as well as led to increased activity of caspase-3 and apoptosis. Treatment with LAQ824 also down-regulated the levels of Bcl-2, Bcl-x(L), XIAP, and survivin. Partial inhibition of apoptosis due to LAQ824 or Apo- 2L/TRAIL exerted by Bcl-2 overexpression was reversed by cotreatment with LAQ824 and Apo-2L/ TRAIL.

Significantly, cotreatment with LAQ824 increased Apo-2L/TRAIL-induced apoptosis of primary acute myelogenous leukemia blast samples isolated from 10 patients with acute myelogenous leukemia. Taken together, these findings indicate that LAQ824 may have promising activity in augmenting Apo-2L/TRAIL-induced death-inducing signaling complex and apoptosis of human acute leukemia cells.

L57 ANSWER 46 OF 59 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2004570288 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15542778
TITLE: The histone deacetylase inhibitor FR901228 induces caspase-dependent apoptosis via the mitochondrial pathway in small cell lung cancer cells.
AUTHOR: Doi Seiji; Soda Hiroshi; Oka Mikio; Tsurutani Junji; Kitazaki Takeshi; Nakamura Yoichi; Fukuda Minoru; Yamada Yasuaki; Kamihira Shimeru; Kohno Shigeru
CORPORATE SOURCE: Division of Molecular and Clinical Microbiology, Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
SOURCE: Molecular cancer therapeutics, (2004 Nov) Vol. 3, No. 11, pp. 1397-402.
Journal code: 101132535. ISSN: 1535-7163.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 16 Nov 2004
Last Updated on STN: 3 May 2005
Entered Medline: 2 May 2005

AB Histone deacetylase inhibitors modulate the transcription of target genes and represent a new class of anticancer agents. The histone deacetylase inhibitor FR901228 has been reported to show antiproliferative and apoptotic effects in various malignancies including small cell lung cancer (SCLC) in vitro; however, the underlying mechanism is not fully understood. BCL-2 and BCL-XL are antiapoptotic proteins, of which overexpression has been reported to confer resistance to anticancer agents. High levels of BCL-2 and BCL-XL are frequently expressed in SCLC tumors. The present study was designed to clarify the apoptotic pathway of FR901228 in SCLC cells in vitro. FR901228 induced apoptosis in three SCLC cell lines after 24 hours of treatment. FR901228 activated caspase-9 and caspase-3 but not caspase- 8, and the caspase-3 inhibitor Z-DEVD-fmk blocked the cytotoxicity of FR901228. FR901228 down-regulated the expression of bcl-2 and bcl-xL mRNA through de novo protein synthesis and suppressed the expression of BCL-2 and BCL-XL proteins. In addition, the combination of bcl-2 antisense oligonucleotides with FR901228 enhanced FR901228-induced caspase-3 activity and cytotoxicity. These findings suggest that FR901228 induces caspase-dependent apoptosis via the mitochondrial pathway rather than the death receptor pathway. Considering the possible contributions of BCL-2 and BCL-XL to multidrug resistance, FR901228 is a promising agent in the treatment of refractory as well as primary SCLC tumors .

L57 ANSWER 47 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:479434 BIOSIS Full-text
DOCUMENT NUMBER: PREV200510271338
TITLE: Human monoclonal antibodies to TRAIL

receptors R1 and R2 effectively induce apoptosis in human myeloma cells.

AUTHOR(S): Ozaki, Shuji [Reprint Author]; Sekimoto, Etsuko; Tanaka, Yoichi; Ohshima, Takashi; Shibata, Hironobu; Hashimoto, Toshihiro; Abe, Masahiro; Motoki, Kazuhiro; Ishida, Isao; Kataoka, Shiro; Matsumoto, Toshio

CORPORATE SOURCE: Univ Tokushima, Grad Sch Med, Dept Med and Bioregulatory Sci, Tokushima 770, Japan

SOURCE: Blood, (NOV 16 2004) Vol. 104, No. 11, Part 1, pp. 919A.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005

AB Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a potent activator of apoptotic pathway in a variety of tumor cells but not normal cells.Therefore, TRAIL and its receptors have been considered as possible therapeutic targets in cancer treatment. However, several myeloma cells were resistant to TRAIL-induced apoptosis depending on the expression patterns of TRAIL receptors including TRAIL-R I and -R2 death receptors, and TRAIL-R3 and -R4 decoy receptors. To explore the contribution of each TRAIL receptor to apoptosis induction of myeloma cells, we generated fully human monoclonal antibodies (MoAbs)that bind specifically to TRAIL-RI and TRAIL-R2 using KM mice that possess the human chromosome fragments containing human immunoglobulin heavy chain loci and YAC transgene containing human kappa light chain gene, Several myeloma cell lines as well as freshly isolated myeloma cells were cultured with TRAIL or these MoAbs in the presence of F(ab'), goat anti-human IgG. Soluble TRAIL (1000 ng/mL) showed more than 80% of cytotoxicity in RPMI 8226 and KMS 12-BM cellswithin 24 hours. However, U266, HS-Sultan, and ARH-77 cells were relatively resistant to TRAIL with maximal cytotoxicity of only 3-31 %. In contrast, anti-TRAIL-R1 MoAb (RI-B 12) effectively induced apoptosis even in TRAIL-resistant myeloma cell lines in a time- and dose-dependent manner with maximal cytotoxicity of 65-99%. This apoptotic response of myeloma cells was confirmed by caspase activation and annexin V binding. On the other hand, anti-TRAIL-R2 MoAb (R2-E11) was less effective against these myeloma cell lines showing 1-33% of cytotoxicity. Among 10 primary myeloma cells, R1-B12 induced at least 10% of cytotoxicity in 7 samples and R2-E11 showed in 3 samples. Flow cytometric analysisdemonstrated that TRAIL-R1 was expressed at a higher level than TRAIL-R2 on these myeloma cell lines and specific mean fluorescence intensity (MFI) was 3.8-7.9 and 1.6-4.2, respectively. TRAIL-R I and -R2 were also detected on primary myeloma cells at low levels and specific MFI was 1.0-2.0 and 1.0-1.6, respectively. Thus, the sensitivity to R1-B12 and R2-E11 was correlated with the expression level of TRAIL-R I and -R2 on cell surface. Treatment of proteasome inhibitor bortezomib and historic deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) did not increase the cell surface expression of TRAIL-RIand -R2 in myeloma cells. However, bortezomib and SAHA induced reduction of cellular FLICE inhibitory protein (c-FLIP) and synergistically enhanced the effect of R1-B12 but not of R2-E11 on apoptosis induction of TRAIL-resistant U266cells. These results suggest that TRAIL-RI mainly contribute to TRAIL-inducedapoptosis in myeloma cells and that R1-B12 may have the therapeutic potentialin combination with bortezomib or HDAC inhibitors in patients with multiple myeloma.

L57 ANSWER 48 OF 59 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 2004631466 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15608694
TITLE: Histone deacetylase inhibitors potentiate TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in lymphoid malignancies.
AUTHOR: Inoue S; MacFarlane M; Harper N; Wheat L M C; Dyer M J S; Cohen G M
CORPORATE SOURCE: MRC Toxicology Unit, Hodgkin Building, University of Leicester, PO Box 138, Lancaster Road, Leicester LE1 9HN, UK.
SOURCE: Cell death and differentiation, (2004 Dec) Vol. 11 Suppl 2, pp. S193-206.
Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 21 Dec 2004
Last Updated on STN: 10 Jun 2005
Entered Medline: 9 Jun 2005

AB New therapies are required for chronic lymphocytic leukemia (CLL), an incurable disease characterized by failure of mature lymphocytes to undergo apoptosis. Activation of cell surface death receptors, such as via TRAIL receptor ligation, may provide a novel therapeutic target for various malignancies. However, CLL and other lymphoid malignancies are resistant to TRAIL. We report that low concentrations of histone deacetylase (HDAC) inhibitors, such as depsipeptide, which alone failed to induce apoptosis, markedly sensitize CLL cells and other primary lymphoid malignancies to TRAIL-induced apoptosis. These combinations caused little or no toxicity to normal lymphocytes. HDAC inhibitors sensitized resistant cells to TRAIL-induced apoptosis by facilitating formation of an active death-inducing signalling complex (DISC), leading to the rapid activation of caspase-8 . The facilitated DISC formation also occurred in the absence of TRAIL-R2 upregulation. Thus, the combination of HDAC inhibitors and TRAIL may be valuable in the treatment of various hemopoietic malignancies.

L57 ANSWER 49 OF 59 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004245744 EMBASE Full-text
TITLE: Enhancement of therapeutic potential of TRAIL by cancer chemotherapy and irradiation: Mechanisms and clinical implications.
AUTHOR: Shankar, Sharmila; Srivastava, Rakesh K. (correspondence)
CORPORATE SOURCE: Dept. of Pharmaceutical Sciences, Greenebaum Cancer Center, Univ. of Maryland School of Pharmacy, 20 N. Pine Street, Baltimore, MD 21201, United States. rsrivast@rx.umaryland.edu
SOURCE: Drug Resistance Updates, (Apr 2004) Vol. 7, No. 2, pp. 139-156.
Refs: 224
ISSN: 1368-7646 CODEN: DRUPFW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)

FILE SEGMENT: 014 Radiology
016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jun 2004
Last Updated on STN: 28 Jun 2004

AB Activation of cell surface death receptors by their cognate ligands triggers apoptosis. Several human death receptors (Fas, TNF-R1, TRAMP, DR4, DR5, DR6, EDA-R and NGF-R) have been identified. The most promising cytokine for anticancer therapy is TRAIL/APO-2L, which induces apoptosis in cancer cells by binding to death receptors TRAIL-R1/DR4 and TRAIL-R2/DR5. The cytotoxic activity of TRAIL is relatively selective to cancer cells compared to normal cells. Signaling by TRAIL and its receptors is tightly regulated process essential for key physiological functions in a variety of organs, as well as the maintenance of immune homeostasis. Despite early promising results, recent studies have identified several TRAIL-resistant cancer cells of various origins. Based on molecular analysis of death-receptor signaling pathways several new approaches have been developed to increase the efficacy of TRAIL. Resistance of cancer cells to TRAIL appears to occur through the modulation of various molecular targets. They may include differential expression of death receptors, constitutively active Akt and NFκB, overexpression of cFLIP and IAPs, mutations in Bax and Bak genes, and defects in the release of mitochondrial proteins in resistant cells. Conventional chemotherapeutic and chemopreventive drugs, and irradiation can sensitize TRAIL-resistant cells to undergo apoptosis. Thus, these agents enhance the therapeutic potential of TRAIL in TRAIL-sensitive cells and sensitize TRAIL-resistant cells. TRAIL and TRAIL-receptor antibodies may prove to be useful for cancer therapy, either alone or in association with conventional approaches such as chemotherapy or radiation therapy. This review discusses intracellular mechanisms of TRAIL resistance and various approaches that can be taken to sensitize TRAIL-resistant cancer cells. .COPYRGT. 2004 Elsevier Ltd. All rights reserved.

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ACCESSION NUMBER: 2004520734 EMBASE Full-text
TITLE: Exploiting death receptor signaling pathways for tumor therapy.
AUTHOR: Fulda, Simone; Debatin, Klaus-Michael
CORPORATE SOURCE: University Children's Hospital, Prittwitzstr. 43, 89075 Ulm, Germany. simone.fulda@medizin.uni-ulm.de
SOURCE: Biochimica et Biophysica Acta - Reviews on Cancer, (10 Dec 2004) Vol. 1705, No. 1, pp. 27-41.
Refs: 188
ISSN: 0304-419X CODEN: BBACEU
PUBLISHER IDENT.: S 0304-419X(04)00059-9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 28 Dec 2004
Last Updated on STN: 28 Dec 2004

AB Apoptosis or programmed cell death is a key regulator of physiological growth control and regulation of tissue homeostasis. Tipping the balance between cell death and proliferation in favor of cell survival may result in tumor formation. Moreover, current cancer therapies, e.g. chemotherapy, γ-irradiation, immunotherapy or suicide gene therapy, primarily exert their antitumor effect by triggering an evolutionary conserved apoptosis program in cancer cells. For example, death receptor signaling has been implied to contribute to the efficacy of cancer therapy. Thus, failure to undergo apoptosis in response to anticancer therapy because of defects in death receptor pathways may result in resistance. Further insights into the mechanisms regulating apoptosis in response to anticancer therapy and how cancer cells evade cell death may provide novel opportunities for targeted therapeutics. Thus, agents designed to selectively activate death receptor pathways may enhance the efficacy of conventional therapies and may even overcome some forms of cancer resistance. .COPYRGT. 2004 Elsevier B.V. All rights reserved.

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ACCESSION NUMBER: 2005050783 EMBASE Full-text
TITLE: Histone deacetylase inhibitors potentiate TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in lymphoid malignancies.
AUTHOR: Inoue, S.; MacFarlane, M.; Harper, N.; Wheat, L.M.C.; Dyer, M.J.S.; Cohen, G.M. (correspondence)
CORPORATE SOURCE: MRC Toxicology Unit, University of Leicester, Hodgkin Building, Lancaster Road, Leicester LE1 9HN, United Kingdom. gmc2@le.ac.uk
SOURCE: Cell Death and Differentiation, (Dec 2004) Vol. 11, No. SUPPL. 2, pp. S193-S206.
Refs: 68
ISSN: 1350-9047 CODEN: CDDIEK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Feb 2005
Last Updated on STN: 18 Feb 2005

AB New therapies are required for chronic lymphocytic leukemia (CLL), an incurable disease characterized by failure of mature lymphocytes to undergo apoptosis. Activation of cell surface death receptors, such as via TRAIL receptor ligation, may provide a novel therapeutic target for various malignancies. However, CLL and other lymphoid malignancies are resistant to TRAIL. We report that low concentrations of histone deacetylase (HDAC) inhibitors, such as depsipeptide, which alone failed to induce apoptosis, markedly sensitize CLL cells and other primary lymphoid malignancies to TRAIL-induced apoptosis. These combinations caused little or no toxicity to normal lymphocytes. HDAC inhibitors sensitized resistant cells to TRAIL-induced apoptosis by facilitating formation of an active death-inducing signalling complex (DISC), leading to the rapid activation of caspase-8 . The

facilitated DISC formation also occurred in the absence of TRAIL-R2 upregulation. Thus, the combination of HDAC inhibitors an TRAIL may be valuable in the treatment of various hemopoietic malignancies. .COPYRGT. 2004 Nature Publishing Group All rights reserved.

L57 ANSWER 52 OF 59 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 2003599909 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14647441
TITLE: FR901228 induces tumor regression associated with induction of Fas ligand and activation of Fas signaling in human osteosarcoma cells.
AUTHOR: Imai Tsuyoshi; Adachi Souichi; Nishijo Koichi; Ohgushi Masatoshi; Okada Masayuki; Yasumi Takahiro; Watanabe Ken-ichiro; Nishikomori Ryuta; Nakayama Tomitaka; Yonehara Shin; Toguchida Junya; Nakahata Tatsutoshi
CORPORATE SOURCE: Department of Pediatrics, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
SOURCE: Oncogene, (2003 Dec 18) Vol. 22, No. 58, pp. 9231-42. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 19 Dec 2003
Last Updated on STN: 22 Jan 2004
Entered Medline: 21 Jan 2004

AB We investigated the antitumor effects of FR901228, a HDAC inhibitor, on human osteosarcoma cells, in vitro and in vivo to explore its possible utility in the treatment of pediatric bone cancers. FR901228 caused marked growth inhibition with a 50% inhibitory concentration of 1.2-7.3 nM and induction of apoptosis in all eight osteosarcoma cell lines tested. These effects of FR901228 were also observed in vivo xenograft models on BALB/c nude mice, and treatment with 5.6 mg/kg/day resulting in a >70% reduction in the mean final tumor volume compared with the mean initial tumor volume. TUNEL assays demonstrated extensive apoptosis in tumor sections of mice treated with FR901228. Induction of apoptosis was preceded by increased expression of Fas ligand (FasL) mRNA, resulting in expression of membrane-bound FasL, which was followed by sequential activation of caspase- 8 and -3. The level of apoptosis induction was reduced using a neutralizing anti-FasL antibody and overexpression of either the dominant-negative FADD or the viral FLICE inhibitory protein. Furthermore, treatment with a suboptimal dose of FR901228 greatly sensitized osteosarcoma cells to agonistic anti-Fas antibody-mediated apoptosis. These findings suggest that FR901228 is a highly promising antitumor agent against osteosarcoma, inducing apoptosis by the activation of the Fas/FasL system.

L57 ANSWER 53 OF 59 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 2003523439 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14581377
TITLE: Induction of apoptosis by apicidin, a histone deacetylase inhibitor, via the activation of mitochondria-dependent caspase cascades in human Bcr-Abl-positive leukemia cells.
AUTHOR: Cheong June-Won; Chong So Young; Kim Ji Yeon; Eom Ju In; Jeung Hoi Kyung; Maeng Ho Young; Lee Seung Tae; Min

Yoo Hong
CORPORATE SOURCE: Department of Internal Medicine, Yonsei University College of Medicine, Seoul 120-752, Korea.
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2003 Oct 15) Vol. 9, No. 13, pp. 5018-27.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 7 Nov 2003
Last Updated on STN: 11 Jun 2004
Entered Medline: 10 Jun 2004

AB PURPOSE: Apicidin, a histone deacetylase inhibitor, is a novel cyclic tetrapeptide that exhibits potent antiproliferative activity against various cancer cell lines. The aim of this study was to examine the potential of apicidin to induce apoptosis in human Bcr-Abl-positive leukemia cells and to assess the mechanism of apicidin-induced apoptosis. EXPERIMENTAL DESIGN: Cells were exposed to various concentrations of apicidin for 2-72 h, after which the levels of apoptosis, histone acetylation, mitochondrial damage, caspase activation, and Bcr-Abl expression were assessed. RESULTS: Apicidin induced apoptosis in K562 cells in a concentration- and time-dependent manner. Similarly, apicidin notably induced the apoptosis in the primary leukemic blasts obtained from chronic myelogenous leukemia patients in blast crisis. The acetylated histone H4 levels increased in a concentration-dependent manner in the K562 cells. However, the timing of cell death caused by apicidin did not exactly correlate with the histone deacetylase inhibitory effect. The disruption of the mitochondrial membrane potential, cytochrome c release into the cytosol, and the mitochondrial Bax translocation were notably demonstrated after the apicidin treatment. Apicidin induced the proteolytic cleavage of procaspase-9, -3, -8, and poly(ADP-ribose) polymerase. Pretreatment of the K562 cells with the caspase-3 inhibitor, DEVD-CHO, completely inhibited the apicidin-induced apoptosis, suggesting that apicidin-induced apoptosis was caspase-dependent. The Fas/Fas ligand death receptor pathway was not involved in the apicidin-mediated apoptosis in K562 cells. Pretreatment of the cells with the caspase-9 inhibitor LEHD-fmk abrogated the apicidin- induced cleavage of procaspase-3, -8, and poly(ADP-ribose) polymerase. The p210 Bcr-Abl protein levels were notably decreased after the apicidin treatment, with near complete loss after 48 h. Reverse transcription-PCR assay demonstrated that the Bcr-Abl mRNA level was also remarkably decreased in a time-dependent manner. CONCLUSIONS: These results indicate that apicidin effectively induces the apoptosis of Bcr-Abl-positive leukemia cells through the activation of the mitochondrial pathway-dependent caspase cascades. The down-regulation of Bcr-Abl mRNA might also be one of the mechanisms implicated in the apicidin-mediated apoptosis in the K562 cells. This study provides the rationale to additionally investigate apicidin as a potential therapeutic agent for the drug-resistant Bcr-Abl-positive leukemia cells.

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ACCESSION NUMBER: 2004-0062763 PASCAL Full-text
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Depsipeptide (FR901228) induces histone acetylation and inhibition of histone deacetylase in chronic lymphocytic

leukemia cells concurrent with activation of caspase 8-mediated apoptosis and down-regulation of c-FLIP protein

AUTHOR: ARON Jennifer L.; PARTHUN Mark R.; MARCUCCI Guido; KITADA Shinichi; MONE Andrew P.; DAVIS Melanie E.; TIANSHENG SHEN; MURPHY Timothy; WICKHAM Joseph; KANAKRY Chris; LUCAS David M.; REED John C.; GREVER Michael R.; BYRD John C.

CORPORATE SOURCE: Department of Internal Medicine, the Division of Hematology-Oncology, and the Department of Molecular and Cellular Biochemistry, The Ohio State University, Columbus, United States; The Burnham Institute, Cancer Research Center, La Jolla, CA, United States; Fourth Division of Hematology-Oncology, Brook Army Medical Center, San Antonio, TX, United States

SOURCE: Blood, (2003), 102(2), 652-658, 54 refs.
ISSN: 0006-4971

DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-3178, 354000112179580340
AN 2004-0062763 PASCAL Full-text

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AB Depsipeptide is in clinical trials for chronic lymphocytic leukemia (CLL) on the basis of earlier observations demonstrating selective in vitro activity in CLL. We sought to determine the relationship of histone H3 and H4 acetylation, inhibition of histone deacetylase, and apoptosis observed in CLL cells to justify a pharmacodynamic end point in these clinical trials. We demonstrate that in vitro depsipeptide induces histone H3 and H4 acetylation and histone deacetylase enzyme inhibition at concentrations corresponding to the LC.sub.5.sub.0 (concentration producing 50% cell death) for cultured CLL cells (0.038 μM depsipeptide). The changes in histone acetylation are lysine specific, involving H4 K5, H4 K12, and H3 K9, and to a lesser extent H4 K8, but not H4 K16 or H3 K14. Depsipeptide-induced apoptosis is caspase dependent, selectively involving the tumor necrosis factor (TNF) receptor (extrinsic pathway) initiating caspase 8 and effector caspase 3. Activation of caspase 8 was accompanied by the down-regulation of cellular FLICE-inhibitory protein (c-FLIP, I-FLICE) without evidence of Fas (CD95) up-regulation. Changes in other apoptotic proteins, including Bcl-2, Bax, Mcl-1, and X-linked inhibitor of apoptosis (XIAP), were not observed. Our results demonstrate a relationship between target enzyme inhibition of histone deacetylase, histone H3 and H4 acetylation, and apoptosis involving the TNF-receptor pathway of apoptosis that is not used by other therapeutic agents in CLL. These data suggest use of histone H3 and H4 acetylation, inhibition of histone deacetylase, and down-regulation of FLIP as pharmacodynamic end points for further evaluation of this drug in patients.

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ACCESSION NUMBER: 2004:151490 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400147516

TITLE: Involvement of the tumor necrosis factor (TNF)/TNF receptor system in leukemic cell apoptosis induced by histone deacetylase inhibitor depsipeptide (FK228).

AUTHOR(S): Sutheesophon, Krittaya [Reprint Author]; Nishimura,

Noriko [Reprint Author]; Furukawa, Yutaka [Reprint Author]; Ishii, Hideshi [Reprint Author]; Kano, Yasuhiko; Kawano, Mikihiko; Ito, Kouichi; Furukawa, Yusuke [Reprint Author]
CORPORATE SOURCE: Division of Stem Cell Regulation, Jichi Medical School, Tochigi, Japan
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 595a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Accumulating evidence suggests that histone deacetylases (HDACs) are involved in leukemogenesis. Various leukemic fusion proteins, including PML/RARalpha and AML-1/ETO, form a complex with HDACs, which aberrantly suppress the expression of genes required for cell differentiation and growth control, leading to the transformation of primitive hematopoietic cells. Specific inhibitors for HDACs are therefore expected to set a novel strategy for the treatment of leukemia called "transcription therapy". Depsipeptide (FK228) is an HDAC inhibitor currently under phase II trials for hematologic malignancies. In this study, we investigated the mechanisms of anti-leukemic effects of depsipeptide using leukemic cell lines such as HL-60, K562, Daudi, and Raji. Depsipeptide at 20 nM induced cell cycle arrest and apoptosis after 24 and 48 hours of culture, respectively, in these cell lines. We then prepared poly (A) RNA from untreated and depsipeptide-treated HL-60 cells after 6 h of culture, and performed DNA chip analysis using IntelliGene human cancer CHIP version 3.0 (Takara Bio Co. Ltd., Shiga, Japan), which contains cDNA fragments of 641 known cancer-related genes. Depsipeptide up-regulated the mRNA expression more than 2.5 fold in 8 genes, and induced the expression of 117 genes. The former includes TNF-alpha, and the latter includes caspases-7 and-10, TRAF-6, TNF2 and TNF10b receptor, suggesting the involvement of the TNF/TNF receptor system in the cytotoxic action of depsipeptide. The increase in TNF-alpha mRNA expression and intracellular TNF-alpha was confirmed by Northern blotting and flow cytometry in HL-60 cells, and was also observed in K562 cells but not in Daudi and Raji cells. The presence of type I TNF receptor (TNF-RI) was detected in HL-60 and K562 cells, raising the possibility of the presence of TNF autocrine loop. Indeed, depsipeptide activated caspases-8 and -10 after 24 h, followed by the cleavage of procaspases-3 and -7. Furthermore, the cytotoxicity of depsipeptide was at least partially inhibited by anti-TNF-alpha neutralizing antibody. Finally, we examined the mechanisms of the enhanced production of TNF-alpha, and found that depsipeptide greatly activated the transcription of the TNF-alpha gene through hyperacetylation of histone tails in its promoter region (-208 to +35). These results indicate that autocrine production of TNF-alpha plays a role in cytotoxicity of depsipeptide against some leukemic cells.

L57 ANSWER 56 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:151486 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400147514
TITLE: Combined treatment with histone deacetylase inhibitor LAQ824 and Apo-2L/TRAIL: Mechanistic basis of

superior activity against human acute leukemia and CML-BC cells.

AUTHOR(S): Li, Yunqing [Reprint Author]; Quo, Fei [Reprint Author]; Sigua, Celia [Reprint Author]; Tao, Jianguo [Reprint Author]; Bali, Purva [Reprint Author]; Vishvanath, Anasuya [Reprint Author]; Gutti, Ravi [Reprint Author]; George, Prince [Reprint Author]; Moscinski, Lynn [Reprint Author]; Atadja, Peter; Bhalla, Kapil N. [Reprint Author]

CORPORATE SOURCE: Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 595a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB In a previous report, we had demonstrated that human AML cells are modestly sensitive, while CML-BC cells are highly resistant to Apo-2L/TRAIL-induced apoptosis (Blood 96:3900, 2000, and Clin Cancer Res 7:350, 2001). Present studies demonstrate that treatment with the histone deacetylases (HDAC) inhibitor (HDI) LAQ824 (50 to 250 nM for 24 to 48 hours) (Novartis Pharmaceuticals Corp.), a cinnamic acid hydroxamate, increased the acetylation of histones H3 and H4, as well as induced p21WAF1 in the human chronic myeloid leukemia blast crisis (CML-BC) K562 and LAMA-84 cells, as well as in T cell acute leukemia Jurkat, B lymphoblast SKW 6.4 and AML HL-60 cells. This was associated with increased accumulation of the cells in the G1 phase of the cell cycle, and was accompanied by the processing and activity of caspase-9 and -3, resulting in apoptosis. Exposure to LAQ824 decreased Bcr-Abl, p-(phosphor) AKT, p-ERK1/2 and Bcl-xL levels in CML-BC cells. LAQ824 treatment also increased the mRNA and protein expressions of the death receptors DR5 and/or DR4, but reduced the mRNA and protein levels of c-FLIP. As compared to treatment with Apo-2L/ TRAIL (100 ng/ml) or LAQ824 alone, pre-treatment with LAQ824 increased the assembly of FADD and caspase-8, but not of c-FLIP, into the Apo-2L/TRAIL -induced death inducing signaling complex (DISC). This was associated with increased processing of caspase-8 followed by BID, cytosolic accumulation of the pro-death molecules cytochrome-c, Smac and Omi, as well as resulting in increased activity of caspase-3. Treatment with LAQ824 also down regulated the levels of Bcl-2, XIAP and survival. This was not reversed by co-treatment with either a pan-caspase or proteasome inhibitor. Combined treatment with LAQ824 and Apo-2L/TRAIL induced more apoptosis of the CML-BC and acute leukemia cells than either agent alone ($p<0.05$). Partial inhibition of apoptosis exerted by Bcl-2 over-expression was reversed by co-treatment with LAQ824 and Apo-2L/TRAIL. Significantly, co-treatment with LAQ824 and Apo-2L/TRAIL induced more apoptosis of primary AML and CML-BC blast samples than either agent alone ($p<0.05$). Taken together, these findings indicate that LAQ824 increases not only Apo-2L/TRAIL-induced DISC activity, but also down-modulates the levels of Bcr-Abl and mitochondria-based Bcl-2 and Bcl-xL as well as the down stream XIAP and survivin. These modulations due to LAQ824 treatment lower the threshold for Apo-2L/TRAIL-induced apoptosis of

human CML-BC and acute leukemia cells. These studies clearly highlight the promising pre-clinical anti-leukemia activity and its mechanistic basis, of the combination of LAQ824 and Apo-2L/TRAIL.

L57 ANSWER 57 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:441944 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300441944
TITLE: Co-treatment with histone deacetylase inhibitors suberoylanilide hydroxamic acid (SAHA) enhances Apo-2L/TRAIL-induced death inducing signaling complex and apoptosis of human acute lymphoid leukemia cells.
AUTHOR(S): Guo, Fei [Reprint Author]; Tao, Jianguo [Reprint Author]; Wittmann, Sylvie [Reprint Author]; Bali, Purva [Reprint Author]; Bhalla, Kapil N. [Reprint Author]
CORPORATE SOURCE: H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 154. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003

L57 ANSWER 58 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:368086 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300368086
TITLE: Co-Treatment with the Histone Deacetylase Inhibitor Suberoylanilide Hydroxamic Acid (SAHA) Enhances Apo-2L/TRAIL-Induced Death Inducing Signaling Complex and Apoptosis of Human Acute Lymphoid Leukemia Cells.
AUTHOR(S): Fei, Guo [Reprint Author]; Wittmann, Sylvie [Reprint Author]; Richon, Victoria [Reprint Author]; Bhalla, Kapil [Reprint Author]
CORPORATE SOURCE: Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 4602. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 2003
Last Updated on STN: 18 Sep 2003

AB SAHA (Suberoylanilide hydroxamic acid) is a known inhibitor of histone deacetylases (HDACs), which catalyze deacetylation of amino terminal lysine residues of the core nucleosomal histones, an activity implicated in chromatin remodeling and the transcriptional regulation of cell-cycle and differentiation regulatory genes, e.g., p21 and p27. Previous studies from our laboratory have demonstrated that human acute leukemia cells express death receptor DR5 and are sensitive to Apo-2L/TRAIL-induced death inducing complex (DISC) and apoptosis. In the present studies we determined the effect of exposure to SAHA on the expression of DR5, as well as on Apo-2L/TRAIL -induced DISC and apoptosis of B lymphoblast SKW6.4 and Jurkat T leukemia cells. Treatment with SAHA (2.0 to 5.0 muM for 24 to 48 hours) significantly increased the mRNA and protein expressions of DR5 and Apo-2L/TRAIL, as determined by a multi-probe RNase protection assay and immunoblot analyses, and induced apoptosis of SKW6.4 and Jurkat cells in a dose dependent manner. This was associated with downregulation of the protein levels of FLIP, XIAP, cIAP1, survivin and Bcl-xL. SAHA treatment induced histone H3 hyperacetylation and p27 expression in SKW6.4 and Jurkat cells, but induced p21 protein levels alone in SKW6.4 cells. In contrast, treatment with SAHA induced cell-cycle G1 phase accumulation of both cell-types. As compared to treatment with SAHA or Apo-2L/TRAIL (100 ng/ml for 24 hours) alone, co-treatment with SAHA and Apo-2L/ TRAIL (for 24 hours) induced significantly more PARP-cleavage activity of caspase-3 and apoptosis of SKW6.4 and Jurkat cells ($p<0.05$). This was associated with significantly increased recruitment of FADD and caspase-8 into Apo -2L/TRAIL-induced DISC, incorporating oligomerized DR5. Apoptosis induced by SAHA and/or Apo- 2L/TRAIL was significantly inhibited by co-treatment with DR5:Fc ($p<0.05$), indicating that SAHA-induced expression of Apo-2L/TRAIL and DR5 were mechanistically involved in SAHA-induced apoptosis of SKW6.4 and Jurkat cells. Taken together, these findings indicate that treatment with SAHA induces the expression of DR5 and Apo-2L/TRAIL, as well as sensitizes human lymphoid leukemia cells to Apo- 2L/TRAIL-induced DISC and apoptosis. They also suggest that co-treatment with SAHA and Apo- 2L/TRAIL may be a promising therapeutic strategy that should be tested against human acute lymphoid leukemia.

L57 ANSWER 59 OF 59 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:129863 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200129863
TITLE: Exposure of human myeloid leukemia cells to the histone deacetylase inhibitor sodium butyrate in combination with the phorbol PMA induces mitochondrial damage and apoptosis through a TNF-dependent pathway.
AUTHOR(S): Rahmani, Mohamed [Reprint author]; Grant, Steven [Reprint author]
CORPORATE SOURCE: Medicine, Medical College of Virginia, Richmond, VA, USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 102a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English

ENTRY DATE: Entered STN: 6 Feb 2002
Last Updated on STN: 26 Feb 2002

AB The histone deacyetylase inhibitor (HDI) sodium butyrate (SB) and the PKC activator phorbol 12-myristate 13-acetate (PMA) are known to induce maturation in human myeloid leukemia cells (U937 and HL-60). The purpose of this study was to determine whether co-treatment with PMA/SB would lower the maturation threshold in leukemic cells exposed to these agents, thereby resulting in potentiation of leukemic cell differentiation. To test this possibility, U937 cells were exposed to 1 mM SB for 28 hr in the presence or absence of a very low concentration of PMA (1 or 2 nM), after which differentiation and apoptosis were monitored. Contrary to expectations, co-treatment with SB and PMA reduced rather than enhanced maturation, manifested by diminution in expression of CD11b and reduced plastic adherence. However, while these SB and PMA concentrations were minimally toxic by themselves, co-exposure of U937 cells to both agents resulted in a marked increase in mitochondrial damage (loss of DELTAPSIm and cytochrome c release), caspase -3, -8, and Bid activation, PARP cleavage, and morphological evidence of apoptosis. The combination of SB and PMA resulted in enhanced induction of p21CIP1, activation of p34cdc2, and down-regulation of cyclin A. SB/PMA-induced apoptosis was blocked by treatment of cells with the PKC inhibitor GFX (1 muM), and substantially diminished by ectopic expression of CrmA or dominant-negative caspase-8. Enhanced apoptosis was also noted in the case of HL-60 cells and in cells exposed to combinations of PMA and other HDIs(e.g., trichostatin, SAHA). Interestingly, SB/PMA-mediated cytochrome c release was diminished by the broad caspase inhibitor Boc-fmk and the caspase-8 inhibitor IETD-fmk. The lethality of the SB/PMA combination was also substantially attenuated by administration of soluble TNF receptor (STNFR) or by anti- TNF antibodies. Collectively, these findings indicate that co-administration of the PKC activator PMA and the HDI SB do not promote myeloid leukemia cell maturation, but instead result in a marked increase in mitochondrial damage and apoptosis. They also suggest that these events proceed through a pathway that is at least partly TNF-dependent.

FILE 'MEDLINE' ENTERED AT 16:09:42 ON 19 AUG 2008

FILE LAST UPDATED: 16 Aug 2008 (20080816/UP). FILE COVERS 1949 TO DATE.

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See HELP RANGE before carrying out any RANGE search.

L59 736 SEA FILE=MEDLINE ABB=ON PLU=ON ("RECEPTORS, TNF-RELATED APOPTOSIS-INDUCING LIGAND"/CT OR D12.776.543.750.705.852.760.396./CT OR D12.776.543.750.73.600./CT)
L60 4831 SEA FILE=MEDLINE ABB=ON PLU=ON ("HISTONE DEACETYLASES"/CT OR D8.811.277.87.520./CT)
L61 2410 SEA FILE=MEDLINE ABB=ON PLU=ON L60(L)AI/CT
L62 13 SEA FILE=MEDLINE ABB=ON PLU=ON L59 AND L61

AI-antagonists & inhibitors

L62 ANSWER 1 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2007657264 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17982666
TITLE: Differential response of p53 and p21 on HDAC inhibitor-mediated apoptosis in HCT116 colon cancer cells in vitro and in vivo.
AUTHOR: Zopf Steffen; Neureiter Daniel; Bouralexis Steve; Abt

Tobias; Glaser Keith B; Okamoto Kinya; Ganslmayer Marion; Hahn Eckhart G; Herold Christoph; Ocker Matthias
CORPORATE SOURCE: Department of Medicine 1, University Hospital Erlangen, D-91054, Erlangen, Germany.
SOURCE: International journal of oncology, (2007 Dec) Vol. 31, No. 6, pp. 1391-402.
Journal code: 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200801
ENTRY DATE: Entered STN: 6 Nov 2007
Last Updated on STN: 16 Jan 2008
Entered Medline: 15 Jan 2008
ED Entered STN: 6 Nov 2007
Last Updated on STN: 16 Jan 2008
Entered Medline: 15 Jan 2008
AB We investigated the effect of a novel histone deacetylase inhibitor, A-423378.0, on the colon carcinoma cell line HCT116 and genetically modified derivatives lacking either p21(cip1/waf1) or p53. HCT116 cell lines were incubated with A-423378.0 at different concentrations for 3-120 h. Cell viability, proliferation and apoptosis rates were determined and verified by western blot, detection of mitochondrial membrane potential breakdown DeltaPsi(m), activation of caspases-3, -8 and cytokeratin 18 cleavage. A subcutaneous xenograft model was established in NMRI mice with daily intraperitoneal injections of 10 mg/kg for 14 days. All three HCT116 cell lines responded to A-423378.0 treatment in a dose- and time-dependent manner via induction of apoptosis as measured by breakdown of DeltaPsi(m) and BrdU incorporation. We identified that A-423378.0 induced the expression of TRAIL and TRAIL receptor, especially TRAIL-R2/hDR5, which was up-regulated in HCT116 cells after treatment with A-423378.0. In vivo, a growth inhibitory effect was observed with HDAC-I treatment, which was paralleled by a down-regulation of PCNA and a concomitant induction of apoptosis. Treatment of wild-type or knock-out HCT116 cells with A-423378.0 exerts potent anti-proliferative and pro-apoptotic effects in vitro and in vivo. A-423378.0 was able to induce apoptosis in both p21(WAF1) and p53 deficient tumour cells, which appeared to be mediated by the intrinsic cell death pathway. Interestingly, the effects of A-423378.0 on the extrinsic cell death pathway through activation of TRAIL and its signalling pathway indicate that A-423378.0 may be a potent new therapeutic compound for the treatment of advanced colorectal cancer.

L62 ANSWER 2 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2007652668 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17705261
TITLE: Increased hepatotoxicity of tumor necrosis factor-related apoptosis-inducing ligand in diseased human liver.
AUTHOR: Volkmann Xandra; Fischer Ute; Bahr Matthias J; Ott Michael; Lehner Frank; Macfarlane Marion; Cohen Gerald M; Manns Michael P; Schulze-Osthoff Klaus; Bantel Heike
CORPORATE SOURCE: Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany.
SOURCE: Hepatology (Baltimore, Md.), (2007 Nov) Vol. 46, No. 5, pp. 1498-508.
Journal code: 8302946. E-ISSN: 1527-3350.

PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200712
ENTRY DATE: Entered STN: 6 Nov 2007
Last Updated on STN: 19 Dec 2007
Entered Medline: 18 Dec 2007
ED Entered STN: 6 Nov 2007
Last Updated on STN: 19 Dec 2007
Entered Medline: 18 Dec 2007
AB Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis in tumor cells but not in most normal cells and has therefore been proposed as a promising antitumor agent. Recent experiments suggested that isolated primary human hepatocytes but not monkey liver cells are susceptible to certain TRAIL agonists, raising concerns about the use of TRAIL in cancer treatment. Whether TRAIL indeed exerts hepatotoxicity in vivo and how this is influenced by chemotherapeutic drugs or liver disease are completely unknown. Employing different forms of recombinant TRAIL, we found that the cytokine can induce proapoptotic caspase activity in isolated human hepatocytes. However in marked contrast, these different TRAIL preparations induced little or no cytotoxicity when incubated with tissue explants of fresh healthy liver, an experimental model that may more faithfully mimic the in vivo situation. In healthy liver, TRAIL induced apoptosis only when combined with histone deacetylase inhibitors. Strikingly, however, TRAIL alone triggered massive apoptosis accompanied by caspase activation in tissue explants from patients with liver steatosis or hepatitis C viral infection. This enhanced sensitivity of diseased liver was associated with an increased expression of TRAIL receptors and up-regulation of proapoptotic Bcl-2 proteins. CONCLUSION: These results suggest that clinical trials should be performed with great caution when TRAIL is combined with chemotherapy or administered to patients with inflammatory liver diseases.

L62 ANSWER 3 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2007407760 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17499001
TITLE: HDAC inhibitors induce apoptosis in glucocorticoid-resistant acute lymphatic leukemia cells despite a switch from the extrinsic to the intrinsic death pathway.
AUTHOR: Tsapis Michael; Lieb Michele; Manzo Fabio; Shankaranarayanan Pattabhiraman; Herbrecht Raoul; Lutz Patrick; Gronemeyer Hinrich
CORPORATE SOURCE: Department of Cell Biology and Signal Transduction, Institut de Genetique et de Biologie Moleculaire et Cellulaire (IGBMC)/CNRS/INSERM/ULP, BP 10142, F-67404 Illkirch Cedex, C.U. de Strasbourg, France.
SOURCE: The international journal of biochemistry & cell biology, (2007) Vol. 39, No. 7-8, pp. 1500-9. Electronic Publication: 2007-03-15. Journal code: 9508482. ISSN: 1357-2725.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200710

ENTRY DATE: Entered STN: 14 Jul 2007
Last Updated on STN: 16 Oct 2007
Entered Medline: 15 Oct 2007

ED Entered STN: 14 Jul 2007
Last Updated on STN: 16 Oct 2007
Entered Medline: 15 Oct 2007

AB Inhibitors of histone deacetylases (HDACi's) are promising novel tools for cancer therapy. We have compared the growth inhibitory and apoptogenic potential of the pan-HDACi SAHA and the sub-class I selective HDAC inhibitor MS275, as well as valproic acid (VPA) on glucocorticoid sensitive and resistant B (B-ALL) and T (T-ALL) cell acute lymphoblastic leukemia cells and patients blasts. In contrast, to our previous results with U937 acute myeloid leukemia (AML) cells which showed a similar activity of MS275 and SAHA in growth inhibition and apoptosis induction, both B and T-ALL cells were much more efficiently killed by SAHA and VPA than by MS275. The same relative potency was observed with some patient ALL blasts treated ex vivo. SAHA displayed similar efficacy on glucocorticoid-sensitive and insensitive ALL cells but did not synergize with dexamethasone. In studying mediators of apoptosis we found that the TRAIL receptor DR5 is constitutively expressed in glucocorticoid-sensitive CEM-C7 cells which are also TRAIL sensitive. In contrast, glucocorticoid- insensitive CEM-C1 cells do not express DR5 and are insensitive to TRAIL. However, SAHA induces, in addition to p21(WAF1/CIP1) also re-expression of DR5. Importantly, SAHA-induced apoptosis of CEM-C7 cells operates through initiator caspase 10, while it induces apoptosis of CEM-C1 cells through the intrinsic, as well as through caspase-independent death pathways. Our data suggest that the generation of resistance to glucocorticoids has dramatically altered death signaling in these cells and that SAHA overcomes these restrictions by inducing alternative death pathways.

L62 ANSWER 4 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2006666045 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16729023
TITLE: Upregulation of TRAIL-R2 is not involved in HDACi mediated sensitization to TRAIL-induced apoptosis.
AUTHOR: Inoue S; Twiddy D; Dyer M J S; Cohen G M
SOURCE: Cell death and differentiation, (2006 Dec) Vol. 13, No. 12, pp. 2160-2. Electronic Publication: 2006-05-26. Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Letter
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200702
ENTRY DATE: Entered STN: 15 Nov 2006
Last Updated on STN: 3 Feb 2007
Entered Medline: 2 Feb 2007

ED Entered STN: 15 Nov 2006
Last Updated on STN: 3 Feb 2007
Entered Medline: 2 Feb 2007

L62 ANSWER 5 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2006575296 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17000694
TITLE: Antitumor activity of suberoylanilide hydroxamic acid against thyroid cancer cell lines in vitro and in vivo.
AUTHOR: Luong Quang T; O'Kelly James; Braunstein Glenn D; Hershman Jerome M; Koeffler H Phillip
CORPORATE SOURCE: Department of Medicine and the Samuel Oschin

Comprehensive Cancer Center, Cedars-Sinai Medical Center, University of California at Los Angeles School of Medicine, Los Angeles, California 90048, USA.. trong.luong@gmail.com
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2006 Sep 15) Vol. 12, No. 18, pp. 5570-7.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200612
ENTRY DATE: Entered STN: 29 Sep 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 5 Dec 2006
ED Entered STN: 29 Sep 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 5 Dec 2006
AB PURPOSE: The histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), has multiple antitumor effects against a variety of human cancers. EXPERIMENTAL DESIGN: We treated several anaplastic and papillary thyroid cancer cell lines with SAHA to determine if it could inhibit the growth of these cells in vitro and in vivo. RESULTS: SAHA effectively inhibited 50% clonal growth of the anaplastic thyroid cancer cell lines, ARO and FRO, and the papillary thyroid cancer cell line, BHP 7-13, at 1.3x10(-7) to 5x10(-7) mol/L, doses that are achievable in patients. In concert with growth inhibition, SAHA down-regulated the expression of cyclin D1 and up-regulated levels of p21WAF1. Annexin V and cleavage of poly(ADP)ribose polymerase were both increased by exposure of the thyroid cancer cells to SAHA. Expression of the death receptor 5 (DR5) gene was also increased by SAHA, but the combination of the DR5 ligand, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), with SAHA had little effect compared with SAHA alone. Of note, the combination of paclitaxel, doxorubicin, or paraplatin with SAHA enhanced cell killing of the thyroid cancer cells. In addition, murine studies showed that SAHA administered daily by i.p. injection at 100 mg/kg inhibited the growth of human thyroid tumor cells. CONCLUSION: Our data indicate that SAHA is a plausible adjuvant therapy for thyroid cancers.

L62 ANSWER 6 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2006010422 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16397266
TITLE: Histone deacetylase inhibitors modulate the sensitivity of tumor necrosis factor-related apoptosis-inducing ligand-resistant bladder tumor cells.
AUTHOR: Earel James K Jr; VanOosten Rebecca L; Griffith Thomas S
CORPORATE SOURCE: Department of Urology, Holden Comprehensive Cancer Center, University of Iowa, Iowa City, Iowa 52242-1089, USA.
CONTRACT NUMBER: CA109446 (United States NCI)
SOURCE: Cancer research, (2006 Jan 1) Vol. 66, No. 1, pp. 499-507.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200602
ENTRY DATE: Entered STN: 7 Jan 2006
Last Updated on STN: 28 Feb 2006
Entered Medline: 23 Feb 2006

ED Entered STN: 7 Jan 2006
Last Updated on STN: 28 Feb 2006
Entered Medline: 23 Feb 2006

AB Urothelial carcinoma of the bladder accounts for approximately 5% of all cancer deaths in humans. The large majority of tumors are superficial at diagnosis and, after local surgical therapy, have a high rate of local recurrence and progression. Current treatments extend time to recurrence but do not alter disease survival. The objective of the present study was to investigate the tumoricidal potential of combining the apoptosis-inducing protein tumor necrosis factor-related apoptosis inducing ligand (TRAIL) with histone deacetylase inhibitors (HDACi) against TRAIL-resistant bladder tumor cells. Pretreatment with HDACi at nontoxic doses, followed by incubation with TRAIL, resulted in a marked increase in TRAIL-induced apoptosis of T24 cells but showed no significant increase in toxicity to SV40 immortalized normal human uroepithelial cell-1. HDAC inhibition, especially with sodium butyrate and trichostatin A, led to increased TRAIL-R2 gene transcription that correlated with increased TRAIL-R2 surface expression. The increased TRAIL-R2 levels also resulted in accelerated death-inducing signaling complex (DISC) formation, caspase activation, and loss of mitochondrial membrane potential, which all contributed to the increase in tumor cell death. Collectively, these results show the therapeutic potential of combining HDAC inhibition with TRAIL as an alternative treatment for bladder cancer.

L62 ANSWER 7 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2005625191 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16096370
TITLE: Histone deacetylase inhibitors modulate renal cell carcinoma sensitivity to TRAIL/Apo-2L-induced apoptosis by enhancing TRAIL-R2 expression.
AUTHOR: VanOosten Rebecca L; Moore Jill M; Karacay Bahri; Griffith Thomas S
CORPORATE SOURCE: Department of Urology, University of Iowa, Iowa City, Iowa 52242-1089, USA.
CONTRACT NUMBER: 2 P50 DK052617-06A1 (United States NIDDK)
CA109446-01 (United States NCI)
SOURCE: Cancer biology & therapy, (2005 Oct) Vol. 4, No. 10, pp. 1104-12. Electronic Publication: 2005-10-13.
Journal code: 101137842. ISSN: 1538-4047.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200606
ENTRY DATE: Entered STN: 29 Nov 2005
Last Updated on STN: 23 Jun 2006
Entered Medline: 22 Jun 2006

ED Entered STN: 29 Nov 2005
Last Updated on STN: 23 Jun 2006
Entered Medline: 22 Jun 2006

AB Every year, 12,000 people in the U.S. die from renal cell carcinoma. Current therapies include partial or complete nephrectomy or treatments such as

administration of IFN-alpha and/or interleukins that are moderately effective, at best. Moreover, the current therapies are invasive and inefficient and new therapies are needed. Histone deacetylase (HDAC) inhibitors have recently been found to sensitize cells to apoptosis-inducing agents, although the mechanism of this action is largely unknown. The current study has investigated the potential of using five different histone deacetylase inhibitors (HDACI) (depsipeptide, MS-275, oxamflatin, sodium butyrate, and trichostatin A) to sensitize TNF-related apoptosis-inducing ligand (TRAIL)/Apo-2L-resistant renal cell carcinoma cells to TRAIL/Apo-2L-induced apoptosis. Sodium butyrate and trichostatin A each enhanced TRAIL/Apo-2L-mediated tumor cell death to a greater extent than the other HDACI. Annexin V staining and caspase activity demonstrated the mechanism of cell death was apoptosis. Both sodium butyrate and trichostatin A treatment also increased mRNA and surface expression of TRAIL receptor 2 that was dependent on the transcription factor Sp1, thus providing a possible mechanism behind the increased sensitivity to TRAIL/Apo-2L. These results indicate that combination therapy of HDACI, such as sodium butyrate and trichostatin A, and TRAIL/Apo-2L has great potential for an efficient alternative therapy for renal cell carcinoma.

L62 ANSWER 8 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2005593017 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16273296
TITLE: Interactive effects of histone deacetylase inhibitors and TRAIL on apoptosis in human leukemia cells: involvement of both death receptor and mitochondrial pathways.
AUTHOR: Shankar Sharmila; Singh Thiyam R; Fandy Tamer E; Luetrakul Thitidaj; Ross Douglas D; Srivastava Rakesh K
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Molecular and Cellular Biology Program, University of Maryland, Baltimore, MD 21201-1180, USA.
SOURCE: International journal of molecular medicine, (2005 Dec) Vol. 16, No. 6, pp. 1125-38.
Journal code: 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200602
ENTRY DATE: Entered STN: 8 Nov 2005
Last Updated on STN: 22 Feb 2006
Entered Medline: 21 Feb 2006
ED Entered STN: 8 Nov 2005
Last Updated on STN: 22 Feb 2006
Entered Medline: 21 Feb 2006
AB In the present study, we aimed to elucidate the mechanism responsible for the interactive effects of histone deacetylase (HDAC) inhibitors [suberoylanilide hydroxamic acid (SAHA), MS-275, m-carboxycinnamic acid bishydroxamide (CBHA), and trichostatin-A (TSA)] and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) on apoptosis in leukemia cells. HDAC inhibitors enhance the apoptosis-inducing potential of TRAIL in leukemia cells (HL60, Jurkat, K562, and U937) through multiple mechanisms; up-regulation of DR4, DR5, Bak, Bax, Bim, Noxa and PUMA, down-regulation of IAPs, Mcl-1, Bcl-2, Bcl-XL and cFLIP, release of mitochondrial proteins (cytochrome c, Smac/DIABLO and Omi/Htr2) to the cytosol, induction of p21WAF1/CIP1 and p27KIP1, activation of caspase-3 and cleavage of poly(ADP-ribose) polymerase (PARP). The sequential treatment of cells with HDAC inhibitors followed by TRAIL was more effective in inducing apoptosis than the concurrent treatment or single agent alone.

The up-regulation of death receptors and inhibition of cFLIP by HDAC inhibitors will increase the ability of TRAIL to induce apoptosis, due to enhance activation of caspase-8, cleavage of Bid, and release of mitochondrial proteins to the cytosol, and subsequent activation of caspase-9 and caspase-3. Thus, the combination of HDAC inhibitors and TRAIL can be used as a new therapeutic approach for the treatment of leukemia.

L62 ANSWER 9 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2005174461 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15771957
TITLE: Depsipeptide (FR901228) enhances the cytotoxic activity of TRAIL by redistributing TRAIL receptor to membrane lipid rafts.
AUTHOR: Vanoosten Rebecca L; Moore Jill M; Ludwig Aaron T; Griffith Thomas S
CORPORATE SOURCE: Department of Urology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242-1089, USA.
SOURCE: Molecular therapy : the journal of the American Society of Gene Therapy, (2005 Apr) Vol. 11, No. 4, pp. 542-52. Journal code: 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 6 Apr 2005
Last Updated on STN: 21 Sep 2005
Entered Medline: 20 Sep 2005
ED Entered STN: 6 Apr 2005
Last Updated on STN: 21 Sep 2005
Entered Medline: 20 Sep 2005
AB TRAIL (TNF-related apoptosis-inducing ligand) induces apoptosis in various tumor cell types and is under investigation as a cancer therapeutic. The development of a recombinant adenovirus encoding the full-length human TRAIL gene (Ad5-TRAIL) replaces the need for large quantities of soluble TRAIL protein in tumor suppressive therapies. However, the full potential of Ad5-TRAIL has not yet been maximized. Recent investigation of a histone deacetylase inhibitor, depsipeptide (FR901228), has demonstrated that it increases cellular susceptibility to adenovirus infection and augments adenoviral transgene expression. Thus, studies were initiated to evaluate the ability of depsipeptide to enhance the cytotoxic activity of Ad5-TRAIL against human prostate tumor cells. In vitro, depsipeptide increased expression of coxsackie-adenovirus receptor, leading to increased adenoviral infection and transgene expression. Additionally, tumor cell killing by Ad5-TRAIL was higher following depsipeptide pretreatment. More surprisingly, depsipeptide also increased prostate tumor cell sensitivity to TRAIL-induced apoptosis. Investigation into the mechanism responsible for increased TRAIL responsiveness revealed increased levels of TRAIL-R1 and -R2 in membrane lipid rafts following depsipeptide treatment. These results indicate that depsipeptide is a potent agent for enhancing the activity of Ad5-TRAIL by multiple mechanisms, allowing for a more efficient use of Ad5-TRAIL as an antitumor therapy.

L62 ANSWER 10 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2004631466 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15608694

TITLE: Histone deacetylase inhibitors potentiate TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in lymphoid malignancies.
AUTHOR: Inoue S; MacFarlane M; Harper N; Wheat L M C; Dyer M J S; Cohen G M
CORPORATE SOURCE: MRC Toxicology Unit, Hodgkin Building, University of Leicester, PO Box 138, Lancaster Road, Leicester LE1 9HN, UK.
SOURCE: Cell death and differentiation, (2004 Dec) Vol. 11 Suppl 2, pp. S193-206.
Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 21 Dec 2004
Last Updated on STN: 10 Jun 2005
Entered Medline: 9 Jun 2005
ED Entered STN: 21 Dec 2004
Last Updated on STN: 10 Jun 2005
Entered Medline: 9 Jun 2005
AB New therapies are required for chronic lymphocytic leukemia (CLL), an incurable disease characterized by failure of mature lymphocytes to undergo apoptosis. Activation of cell surface death receptors, such as via TRAIL receptor ligation, may provide a novel therapeutic target for various malignancies. However, CLL and other lymphoid malignancies are resistant to TRAIL. We report that low concentrations of histone deacetylase (HDAC) inhibitors, such as depsipeptide, which alone failed to induce apoptosis, markedly sensitize CLL cells and other primary lymphoid malignancies to TRAIL-induced apoptosis. These combinations caused little or no toxicity to normal lymphocytes. HDAC inhibitors sensitized resistant cells to TRAIL-induced apoptosis by facilitating formation of an active death-inducing signalling complex (DISC), leading to the rapid activation of caspase-8. The facilitated DISC formation also occurred in the absence of TRAIL-R2 upregulation. Thus, the combination of HDAC inhibitors and TRAIL may be valuable in the treatment of various hemopoietic malignancies.

L62 ANSWER 11 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2004474518 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15142888
TITLE: Sodium butyrate sensitizes TRAIL-mediated apoptosis by induction of transcription from the DR5 gene promoter through Sp1 sites in colon cancer cells.
AUTHOR: Kim Young-Ho; Park Jong-Wook; Lee Jai-Youl; Kwon Taeg Kyu
CORPORATE SOURCE: Department of Immunology, School of Medicine, Keimyung University, 194 DongSan-Dong Jung-Gu, Taegu, 700-712, South Korea.
SOURCE: Carcinogenesis, (2004 Oct) Vol. 25, No. 10, pp. 1813-20. Electronic Publication: 2004-05-13.
Journal code: 8008055. ISSN: 0143-3334.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 24 Sep 2004
Last Updated on STN: 10 Nov 2004
Entered Medline: 9 Nov 2004
ED Entered STN: 24 Sep 2004
Last Updated on STN: 10 Nov 2004
Entered Medline: 9 Nov 2004
AB Sodium butyrate, a short-chain fatty acid naturally present in the human colon, is able to induce cell cycle arrest, differentiation and apoptosis in various cancer cells. Sodium butyrate is most probably related to the inhibition of deacetylases leading to hyperacetylation of chromatin components such as histones and non-histone proteins and to alterations in gene expression. In this study, we demonstrate for the first time that sodium butyrate selectively up-regulated DR5 but had no effect on the expression of the other TNF-alpha-related apoptosis-inducing ligand (TRAIL) receptor, DR4. Sodium butyrate-induced expression of DR5 involves the putative Sp1 site within the DR5 promoter region. Using a combination of the electrophoretic mobility shift assay and the luciferase reporter assay, we found that a specific Sp1 site (located at -195 bp relative to the transcription start site) is required for sodium butyrate-mediated activation of the DR5 promoter. When HCT116 cells were incubated with sodium butyrate and TRAIL, enhanced TRAIL-mediated apoptosis was observed. The enhanced apoptosis was measured by fluorescent activated cell sorting analysis, DNA fragmentation, poly (ADP-ribose) polymerase cleavage, down-regulation of XIAP and caspase activity. Taken together, the present studies suggest that sodium butyrate may be an effective sensitizer of TRAIL-induced apoptosis.

L62 ANSWER 12 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2004413578 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15208660
TITLE: Histone deacetylase inhibitors upregulate death receptor 5/TRAIL-R2 and sensitize apoptosis induced by TRAIL/APO2-L in human malignant tumor cells.
AUTHOR: Nakata Susumu; Yoshida Tatsushi; Horinaka Mano; Shiraishi Takumi; Wakada Miki; Sakai Toshiyuki
CORPORATE SOURCE: Department of Molecular-Targeting Cancer Prevention, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramcahi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
SOURCE: Oncogene, (2004 Aug 19) Vol. 23, No. 37, pp. 6261-71. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20 Aug 2004
Last Updated on STN: 10 Sep 2004
Entered Medline: 9 Sep 2004
ED Entered STN: 20 Aug 2004
Last Updated on STN: 10 Sep 2004
Entered Medline: 9 Sep 2004
AB Death receptor 5 (DR5) is a receptor for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). TRAIL is a promising candidate for cancer therapeutics due to its ability to induce apoptosis selectively in cancer cells. Here, we report that histone deacetylase inhibitors (HDACIs) such as trichostatin A (TSA), sodium butyrate, and suberoylanilide hydroxamic acid (SAHA) upregulated DR5 expression in various human malignant tumor cells. An

RNase protection assay demonstrated that HDACIs induced DR5 mRNA markedly but not that of other death receptor family members in Jurkat cells. HDACIs increased DR5 mRNA and protein in a dose- and time-dependent manner. We also show TSA increased DR5 promoter activity using a luciferase promoter assay. Furthermore, we demonstrated that HDACIs strongly sensitized exogenous soluble recombinant human TRAIL-induced apoptosis synergistically in Jurkat and HL-60 cells that were tolerant to TRAIL alone. The combined use of HDACIs and TRAIL in suboptimal concentrations induced Bid cleavage and activation of caspase-8, -10, -3, and -9. Human recombinant DR5/Fc chimera protein, zVAD-fmk pancaspase inhibitor, and caspase-8 and -10 inhibitors efficiently reduced apoptosis induced by cotreatment with HDACIs and TRAIL. Furthermore, TSA did not significantly induce DR5 protein and HDACIs did not enhance TRAIL-induced apoptosis in normal human peripheral blood mononuclear cells. These results suggest that this combined treatment with HDACIs and TRAIL is a promising strategy for new cancer therapeutics.

L62 ANSWER 13 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2004165911 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15059915
TITLE: Cotreatment with histone deacetylase inhibitor LAQ824 enhances Apo-2L/tumor necrosis factor-related apoptosis inducing ligand-induced death inducing signaling complex activity and apoptosis of human acute leukemia cells.
AUTHOR: Guo Fei; Sigua Celia; Tao Jianguo; Bali Purva; George Prince; Li Yunqing; Wittmann Sylvie; Moscinski Lynn; Atadja Peter; Bhalla Kapil
CORPORATE SOURCE: Department of Interdisciplinary Oncology, Moffitt Cancer Center and Research Institute University of South Florida, Tampa, Florida 33612, USA.
SOURCE: Cancer research, (2004 Apr 1) Vol. 64, No. 7, pp. 2580-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 3 Apr 2004
Last Updated on STN: 20 May 2004
Entered Medline: 19 May 2004
ED Entered STN: 3 Apr 2004
Last Updated on STN: 20 May 2004
Entered Medline: 19 May 2004
AB Present studies demonstrate that treatment with the histone deacetylases inhibitor LAQ824, a cinnamic acid hydroxamate, increased the acetylation of histones H3 and H4, as well as induced p21(WAF1) in the human T-cell acute leukemia Jurkat, B lymphoblast SKW 6.4, and acute myelogenous leukemia HL-60 cells. This was associated with increased accumulation of the cells in the G(1) phase of the cell cycle, as well as accompanied by the processing and activity of caspase-9 and -3, and apoptosis. Exposure to LAQ824 increased the mRNA and protein expressions of the death receptors DR5 and/or DR4, but reduced the mRNA and protein levels of cellular FLICE-inhibitory protein (c-FLIP). As compared with treatment with Apo-2L/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or LAQ824 alone, pretreatment with LAQ824 increased the assembly of Fas-associated death domain and caspase-8, but not of c-FLIP, into the Apo-2L/TRAIL-induced death-inducing signaling complex. This increased the processing of caspase-8 and Bcl-2 interacting domain (BID), augmented cytosolic accumulation of the prodeath molecules cytochrome-c, Smac

and Omi, as well as led to increased activity of caspase-3 and apoptosis. Treatment with LAQ824 also down-regulated the levels of Bcl-2, Bcl-x(L), XIAP, and survivin. Partial inhibition of apoptosis due to LAQ824 or Apo-2L/TRAIL exerted by Bcl-2 overexpression was reversed by cotreatment with LAQ824 and Apo-2L/TRAIL. Significantly, cotreatment with LAQ824 increased Apo-2L/TRAIL-induced apoptosis of primary acute myelogenous leukemia blast samples isolated from 10 patients with acute myelogenous leukemia. Taken together, these findings indicate that LAQ824 may have promising activity in augmenting Apo-2L/TRAIL-induced death-inducing signaling complex and apoptosis of human acute leukemia cells.

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED AT 16:20:06 ON 19 AUG 2008)

L63 284 S "ATADJA P"?/AU
L64 1108 S "BHALLA K"?/AU
L65 77 S L63 AND L64
L66 94 S (L63-L65) AND L9
L67 24 S L66 AND L8
L68 3 S (L63-L65) AND L21
L69 25 S L67 OR L68
L70 12 DUP REM L69 (13 DUPLICATES REMOVED)

L70 ANSWER 1 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2008:216038 BIOSIS Full-text
DOCUMENT NUMBER: PREV200800216080
TITLE: Molecular characterization and drug-sensitivity of pan histone deacetylase inhibitor resistant human acute myeloid leukemia cells.
AUTHOR(S): Rao, Rekha [Reprint Author]; Fernandez, Pravina; Herger, Bryan; Yang, Yonghua; Chen, Jianguang; Wang, Yongchao; Mandawat, Aditya; Lee, Pearl; Atadja, Peter; Bhalla, Kapil
CORPORATE SOURCE: MCG Canc Ctr, Coll Med, Augusta, GA USA
SOURCE: Blood, (NOV 16 2007) Vol. 110, No. 11, Part 1, pp. 247A-248A.
Meeting Info.: 49th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 08 -11, 2007. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Mar 2008
Last Updated on STN: 26 Mar 2008

AB Hydroxamic acid,analogue pan-histone deacetylase (HDAC) inhibitors (HA-HDIs), e.g., vorinostat, LAQ824 and LBH589, induce in vitro growth arrest, differentiation and apoptosis of human acute leukemia cells. Continuous and protracted use. of HA-HDI as currently used in the clinic against hematologic malignancies is likely to result in the emergence of HA- HDI resistance in leukemia cells. By continuous in vitro exposure of the AML HL-60 cells to the cinnamic acid analogue HA- HDI LAQ824, we have generated An in vitro and in vivo model of HA-HDI-resistant HL-60/LR cells, which are capable of growth in high concentrations (200 nM) of LAQ824. HL-60/LR versus the parental HL-60 cells have a shorter doubling time (12 versus 24 hours), increased % of cells in the S phase of the cell cycle (62.4 versus 40.0) and exhibit shorter interval to generation of leukemia And survival in NOD/SCID mice. As compared to,HL-60, HL-60/LR cells have-a resistance index of 1.00 for LAQ824, and are cross-resistant to other antileukemia agents exhibiting resistance index for LBH589: 50; trichostatin A: 15; vorinostat: 30; sodium butyrate: 10; etopside:

5.0; Ara-C: 3.3 and TRAIL: 31.3. As compared to. HL-60, HL-60/LR cells express higher levels of Bcl-x(L) and XIAP but lower levels MCL-1. HL-60/LR versus HL-60 cells also express markedly reduced levels of Bim and Bak but higher levels of Bax. Although expressing higher levels of the death receptors (DR) 4 and 5 and lower levels of c-FLIP, HL-60/LR cells lack expression of caspase-8 and show barely detectable levels of FADD. Additionally, HL-60/LR versus HL-60 cells have markedly higher levels of AKT, c-RAF, and p-STAT5. Although expressing higher levels of HDAC1, HDAC2, and HDAC4, HL-60/LR cells lack detectable expression of HDAC6, with increased expression of hyper-acetylated hsp90 and alpha-iubulin- two of the substrates deacetylated by HDAC6. As compared to hsp90 in HL-60 cells, hyper-acetylated hsp90 in HL-60/LR cells exhibits less binding to ATP and p23. Utilizing a polyclonal antibody generated against acetylated hsp90 alpha, confocal immuno-fluorescence microscopy showed higher and mostly cell surface expression of acetylated hsp90 alpha in HL-60/LR versus HL-60 cells. As compared to HL-60, treatment of HL-60/LR cells with LAQ824 failed to induce p21 and hsp70, or increase the levels of hyper-acetylated hsp90 and alpha-tubulin. Notably, although cross-resistant to several anti-leukemia drugs, HL-60/LR cells are collaterally sensitive to the hsp90-inhibiting geldanamycin analogues 17-allylamino-demothoxy geldanamycin (17-AAG) and 17-DMAG with a four and fivefold increased sensitivity to 17-AAG and 17-DMAG, respectively. This was associated with a lack of both a 17-AAG mediated induction of hsp70 and a lesser decline in the levels of AKT and c-RAF in HL-60/LR versus HL-60 cells. Taken together, these findings elucidate several notable in vitro and in vivo biologic characteristics and drug-sensitivity profile of the first fully-characterized HA-HDI-resistant human AML cells. Our findings clearly demonstrate that in vitro resistance to HA- HDIs is associated with loss of HDAC6 expression, hyperacetylation of hsp90, aggressive leukemia phenotype, but cross-sensitivity to 17-AAG. These findings also suggest that hsp90 inhibitors should be tested for overriding de novo or acquired HA- HDI resistance in AML.

L70 ANSWER 2 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:588026 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600598652
TITLE: Synergistic interactions between the HbAC inhibitor NVP-LAQ824 and the nucleoside analog fludarabine in human leukemia cells involve ROS generation and modulation of the NF-kB and JNK pathways.
AUTHOR(S): Rosato, Roberto R. [Reprint Author]; Maggio, Sonia C.; Almenara, Jorge A.; Coe, Stefanie; Rahmani, Mohamed; Dai, Yun; Atadja, Peter; Grant, Steven
CORPORATE SOURCE: Novartis Inst Biomed Res, E Hanover, NJ USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (APR 2006) Vol. 47, pp. 1095. Meeting Info.: 97th Annual Meeting of the American-Association-for-Cancer-Research (AACR). Washington, DC, USA. April 01 -05, 2006. Amer Assoc Canc Res.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Nov 2006
Last Updated on STN: 8 Nov 2006

L70 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2006:43145 HCAPLUS Full-text

DOCUMENT NUMBER: 144:80810
TITLE: The histone deacetylase inhibitor LAQ824 induces human leukemia cell death through a process involving XIAP down-regulation, oxidative injury, and the acid sphingomyelinase-dependent generation of ceramide
AUTHOR(S): Rosato, Roberto R.; Maggio, Sonia C.; Almenara, Jorge A.; Payne, Shawn G.; Atadja, Peter ; Spiegel, Sarah; Dent, Paul; Grant, Steven
CORPORATE SOURCE: Department of Medicine, Virginia Commonwealth University, Richmond, VA, USA
SOURCE: Molecular Pharmacology (2006), 69(1), 216-225
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Determinants of differentiation and apoptosis induction by the novel histone deacetylase inhibitor (HDACI) LAQ824 were examined in human leukemia cells (U937 and Jurkat). Exposure of U937 cells to a low concentration of LAQ824 (30 nM) resulted in a delayed (2 h) increase in reactive oxygen species (ROS), induction of p21WAF1/CIP1, pRb dephosphorylation, growth arrest of cells in G0/G1 phase, and differentiation. On the other hand, exposure of cells to a higher concentration of LAQ824 (75 nM) resulted in the early (30 min) generation of ROS, arrest of cells in G2/M phase, down-regulation of XIAP (at the transcriptional level) and Mcl-1 (through a caspase-mediated process), the acid sphingomyelinase-dependent generation of ceramide, and profound mitochondrial injury, caspase activation, and apoptosis. LAQ824-induced lethality in U937 cells did not involve the extrinsic apoptotic pathway, nor was it associated with death receptor up-regulation; instead, it was markedly inhibited by ectopic expression of Bcl-2, Bcl-xL, XIAP, and Mcl-1. The free radical scavenger N-acetyl cysteine blocked LAQ824-mediated ROS generation, mitochondrial injury, Mcl-1 down-regulation, ceramide generation, and apoptosis, suggesting a primary role for oxidative injury in LAQ824 lethality. Together, these findings indicate that LAQ824-induced lethality represents a multifactorial process in which LAQ824-mediated ROS generation is necessary but not sufficient to induce apoptosis, and that the degree of XIAP and Mcl-1 down-regulation and ceramide generation dets. whether this agent engages a maturation rather than an apoptotic program.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:259910 HCAPLUS Full-text
DOCUMENT NUMBER: 142:329825
TITLE: Combination of a histone deacetylase inhibitor with a death receptor ligand
INVENTOR(S): Atadja, Peter Wisdom; Bhalla, Kapil N.
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH; University of South Florida Board of Trustees
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005025619	A1	20050324	WO 2004-EP10468	20040917
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004271730	A1	20050324	AU 2004-271730	20040917
CA 2539000	A1	20050324	CA 2004-2539000	20040917
EP 1667720	A1	20060614	EP 2004-765360	20040917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1852737	A	20061025	CN 2004-80026541	20040917
BR 2004014506	A	20061107	BR 2004-14506	20040917
JP 2007505860	T	20070315	JP 2006-526597	20040917
IN 2006CN00926	A	20070615	IN 2006-CN926	20060316
MX 2006PA03127	A	20061017	MX 2006-PA3127	20060317
US 20070258972	A1	20071108	US 2007-571734	20070319
PRIORITY APPLN. INFO.:			US 2003-504655P P	20030918
			WO 2004-EP10468 W	20040917

OTHER SOURCE(S): MARPAT 142:329825

AB The invention relates to a method of preventing or treating proliferative diseases such as cancer in a mammal, particularly a human, with a combination of pharmaceutical agents which comprises: (a) a histone deacetylase inhibitor (HDAI); and (b) a death receptor ligand. The invention further relates to pharmaceutical compns. comprising: (a) an HDAI; (b) death receptor ligand; and (c) a pharmaceutically acceptable carrier. The present invention further relates to a com. package or product comprising: (a) a pharmaceutical formulation of an HDAI; and (b) a pharmaceutical formulation of death receptor ligand for simultaneous, concurrent, sep. or sequential use.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:120673 HCAPLUS Full-text
DOCUMENT NUMBER: 142:191227
TITLE: Leukemia treatment method and composition
INVENTOR(S): Bhalla, Kapil N.
PATENT ASSIGNEE(S): University of South Florida, USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005011598	A2	20050210	WO 2004-US24774	20040802

WO 2005011598 A3 20050324
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 20070072839 A1 20070329 US 2006-307298 20060131
PRIORITY APPLN. INFO.: US 2003-481163P P 20030731
WO 2004-US24774 A1 20040802

AB A method of inducing high anti-leukemia activity responsive to the combination of hydroxamic acid analog histone deacetylase inhibitors and PKC412 against human acute leukemia characterized as expressing phosphorylated (p)FLT3 kinase by a novel flow cytometry-based assay. Cancer is treated with a histone deacetylase inhibitor and a tyrosine kinase inhibitor. A combination of histone deacetylase inhibitor LAQ824 and FLT3 kinase inhibitor PKC412 was highly active against human acute myelocytic leukemia cells with constitutively active mutant FLT3 tyrosine kinase.

L70 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:513487 HCAPLUS Full-text
DOCUMENT NUMBER: 141:65074
TITLE: Histone deacetylase inhibitor enhancement of TRAIL-induced apoptosis for treatment of leukemia
INVENTOR(S): Bhalla, Kapil N.
PATENT ASSIGNEE(S): University of South Florida, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004052292	A2	20040624	WO 2003-US38881	20031208
WO 2004052292	A3	20050519		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003296310	A1	20040630	AU 2003-296310	20031208

US 20070207119	A1	20070906	US 2005-147112	20050606
PRIORITY APPLN. INFO.:			US 2002-319759P	P 20021206
			WO 2003-US38881	W 20031208

AB Due to the poor long-term clin. outcome in the adult patients with several forms of acute leukemia novel treatment strategies are needed to overcome resistance and sensitize the leukemia blasts to the extrinsic and intrinsic pathway of apoptosis. Treatment with LAQ824 and Apo-2L/TRAIL alone has been recognized to induce apoptosis of leukemia blasts but intrinsic mechanisms of resistance limit the antileukemia activity of either agent when administered alone. The inventive method overcomes the resistance to current apoptosis inducing treatments demonstrated by AML and CML-BC cells by concomitantly administering Apo- 2L/TRAIL with the histone deacetylase inhibitor LAQ824.

L70 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 4

ACCESSION NUMBER:	2004:268089 HCAPLUS Full-text
DOCUMENT NUMBER:	140:385629
TITLE:	Cotreatment with histone deacetylase inhibitor LAQ824 enhances Apo-2L/tumor necrosis factor-related apoptosis inducing ligand-induced death inducing signaling complex activity and apoptosis of human acute leukemia cells
AUTHOR(S):	Guo, Fei; Sigua, Celia; Tao, Jianguo; Bali, Purva; George, Prince; Li, Yunqing; Wittmann, Sylvie; Moscinski, Lynn; Atadja, Peter; Bhalla, Kapil
CORPORATE SOURCE:	Moffitt Cancer Center and Research Institute, Department of Interdisciplinary Oncology, University of South Florida, Tampa, FL, 33612, USA
SOURCE:	Cancer Research (2004), 64(7), 2580-2589 CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER:	American Association for Cancer Research
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Present studies demonstrate that treatment with the histone deacetylases inhibitor LAQ824, a cinnamic acid hydroxamate, increased the acetylation of histones H3 and H4, as well as induced p21WAF1 in the human T-cell acute leukemia Jurkat, B lymphoblast SKW 6.4, and acute myelogenous leukemia HL-60 cells. This was associated with increased accumulation of the cells in the G1 phase of the cell cycle, as well as accompanied by the processing and activity of caspase-9 and -3, and apoptosis. Exposure to LAQ824 increased the mRNA and protein expressions of the death receptors DR5 and/or DR4, but reduced the mRNA and protein levels of cellular FLICE-inhibitory protein (c-FLIP). As compared with treatment with Apo-2L/tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or LAQ824 alone, pretreatment with LAQ824 increased the assembly of Fas-associated death domain and caspase-8, but not of c-FLIP, into the Apo-2L/TRAIL-induced death-inducing signaling complex. This increased the processing of caspase-8 and Bcl-2 interacting domain (BID), augmented cytosolic accumulation of the pro-death mols. cytochrome-c, Smac and Omi, as well as led to increased activity of caspase-3 and apoptosis. Treatment with LAQ824 also down-regulated the levels of Bcl-2, Bcl-xL, XIAP, and survivin. Partial inhibition of apoptosis due to LAQ824 or Apo-2L/TRAIL exerted by Bcl-2 overexpression was reversed by cotreatment with LAQ824 and Apo -2L/TRAIL. Significantly, cotreatment with LAQ824 increased Apo-2L/TRAIL-induced

apoptosis of primary acute myelogenous leukemia blast samples isolated from 10 patients with acute myelogenous leukemia. Taken together, these findings indicate that LAQ824 may have promising activity in augmenting Apo-2L/TRAIL-induced
death-inducing signaling complex and apoptosis of human acute leukemia cells.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 8 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:477239 BIOSIS Full-text
DOCUMENT NUMBER: PREV200510269143
TITLE: Molecular characterization of human AML cells with resistance to growth-inhibitory and apoptotic effects of hydroxamic acid analogue histone deacetylase inhibitors.
AUTHOR(S): Guo, Fei [Reprint Author]; Sigua, Celia; Bali, Purva; Fiskus, Warren; Sondarva, Gautam; Annavarapu, Srinivas; Mouttaki, Abdelmoughite; Atadja, Peter; Bhalla, Kapil N.
CORPORATE SOURCE: H Lee Moffit Canc Ctr and Res Inst, Tampa, FL USA
SOURCE: Blood, (NOV 16 2004) Vol. 104, No. 11, Part 1, pp. 332A.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005

AB The hydroxamic acid analogue (HA) class of historic deacetylase (HDAC) inhibitors (HDIs), e.g., SAHA, LAQ824 and LBH589, are active in inducing growth arrest and apoptosis of human acute and chronic leukemia cells. These agents have been shown to inhibit class I, IIA and IIB HDACs, induce historic H3 and H4 acetylation, increase p21 levels, as well as induce pro-death molecules Bax, Bak and Bim, while attenuating the levels of the antiapoptotic Bcl-x(L), Bcl-2 and XIAR Additionally, treatment with HA-HDIs have also been shown to induce acetylation of the heat shock protein (hsp) 90, thereby inhibiting its ATP binding and chaperone function, which directs the client proteins of hsp90 (e.g., AKT, c-Raf, FLT-3 and Bcr-Abl) to polyubiquitylation and proteasomal degradation. Collectively, these mechanisms explain the anti-leukemia activity ofHA-HDIs. In the present studies, we cultured human AML HL-60 cells in the continuous presence of increasing levels of the cinnamic acid hydroxamate LAQ824,and isolated the HL-60/LR cells that are capable of growth in the continuous presence of 200 nM of LAQ824. HL-60/LR cells were 40 fold more resistant to the cell cycle growth inhibitory and apoptotic effects of LAQ824 than the parental control HL-60 cells, and showed variable degree of cross resistance to the other HA-HDIs, e.g., LBH589 (100 nM) and trichostatin A (250 nM), as well as to phenylbutyrate (3 mM). As compared to the control HL-60, HL-60/LR cells expressed markedly higher levels of Bcl-x(L)-XIAP, AKT and c-Raf, but lower levels of Bak and Bim. Exposure to 200 to 500 nM of LAQ824 for 24 hours induced histone acetylation in both HL-60 and HL-60/LR cells, suggesting that LAQ824 was able to inhibit HDAC activity in both cell types. However, as comparedto HL-60, HL-60/LR cells expressed markedly lower HDAC6 but higher HDAC4 & 10levels, while HDAC2 & 3 levels were similar in the two cell types. LAQ824-induced apoptosis was accompanied with the induction of p21, Bax and Bak and attenuation of Bcl-2, Bcl-x(L) and XIAP levels in the

control HL-60 cells. This was not observed in HL-60/LR cells, which also demonstrated cross-resistance to apoptosis induced by Ara-C (0.5 to 2.0 pM for 48 hours) and TRAIL (100 to 500 ng/ml for 48 hours) but not to the topoisomerase II inhibitor etoposide (up to 2.0 PM). In contrast, HL-60/LR cells were collaterally more sensitive to the hsp90 inhibitor 17-allylaminodemothoxy geldanamycin (17-AAG) (Kosan Biosciences, Hayward, CA) (0.5 to 5.0 mu M for 48 hours). These studies demonstrate that the in vitro resistance of HL-60/LR cells to HA- HDI LAQ824 is associated with perturbations in the levels of specific pro-survival and pro-death proteins. The cross resistance profile and the collateral sensitivity pattern of HL-60/LR cells points to 17-AAG and topoisomerase II inhibitor-based anti-leukemia combinations to override the de-novo or acquired resistance of AML cells to HA-HDIs.

L70 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2004:471697 HCAPLUS Full-text
DOCUMENT NUMBER: 141:46889
TITLE: In bcr-abl-positive myeloid cells resistant to conventional chemotherapeutic agents, expression of Par-4 increases sensitivity to imatinib (STI571) and histone deacetylase -inhibitors
AUTHOR(S): Brieger, Angela; Boehrer, Simone; Schaaf, Simone; Nowak, Daniel; Ruthardt, Martin; Kim, Soo-Zin; Atadja, Peter; Hoelzer, Dieter; Mitrou, Paris S.; Weidmann, Eckhart; Chow, Kai Uwe
CORPORATE SOURCE: Department of Internal Medicine III, Hematology and Oncology, Johann Wolfgang Goethe-University Hospital, Frankfurt am Main, 60590, Germany
SOURCE: Biochemical Pharmacology (2004), 68(1), 85-93
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a variety of malignant cells the prostate-apoptosis-response-gene-4 (Par-4) induces increased sensitivity towards chemotherapeutic agents by down-regulating anti-apoptotic B-cell lymphoma-gene 2 (Bcl-2). Hypothesizing that Par-4 also influences apoptosis in myeloid cell lines, we tested this hypothesis by stably transfecting bcr-abl transformed-K562 cells with a Par-4-expressing vector. Here we demonstrate that over-expression of Par-4 in K562 cells up-regulates expression levels of Bcl-2 and death-associated protein (Daxx). Upon treatment with different chemotherapeutic agents, Fas- or TRAIL agonistic antibodies, Par-4-pos. cells did not exhibit an increased rate of apoptosis as compared to Par-4-neg. control cells. However, incubation with histone deacetylase (HDAC)-inhibitors Trichostatin A (TSA) and LAQ824 or the tyrosine kinase inhibitor Imatinib (STI571) increased the rate of apoptosis in Par-4-pos. K562 cells. Assessing the underlying mol. mechanisms for the Par-4-induced response to HDAC-inhibitors and STI571 we provide evidence, that these effects are associated with a down-regulation of Daxx, enforced activation of caspases and enhanced cleavage of cellular inhibitor of apoptosis (cIAP)-1 and -2.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L70 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:151486 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400147514

TITLE: Combined treatment with histone deacetylase inhibitor LAQ824 and Apo-2L/TRAIL: Mechanistic basis of superior activity against human acute leukemia and CML-BC cells.

AUTHOR(S): Li, Yunqing [Reprint Author]; Quo, Fei [Reprint Author]; Sigua, Celia [Reprint Author]; Tao, Jianguo [Reprint Author]; Bali, Purva [Reprint Author]; Vishvanath, Anasuya [Reprint Author]; Gutti, Ravi [Reprint Author]; George, Prince [Reprint Author]; Moscinski, Lynn [Reprint Author]; Atadja, Peter ; Bhalla, Kapil N. [Reprint Author]

CORPORATE SOURCE: Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 595a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB In a previous report, we had demonstrated that human AML cells are modestly sensitive, while CML-BC cells are highly resistant to Apo-2L/TRAIL-induced apoptosis (Blood 96:3900, 2000, and Clin Cancer Res 7:350, 2001). Present studies demonstrate that treatment with the histone deacetylases (HDAC) inhibitor (HDI) LAQ824 (50 to 250 nM for 24 to 48 hours) (Novartis Pharmaceuticals Corp.), a cinnamic acid hydroxamate, increased the acetylation of histones H3 and H4, as well as induced p21WAF1 in the human chronic myeloid leukemia blast crisis (CML-BC) K562 and LAMA-84 cells, as well as in T cell acute leukemia Jurkat, B lymphoblast SKW 6.4 and AML HL-60 cells. This was associated with increased accumulation of the cells in the G1 phase of the cell cycle, and was accompanied by the processing and activity of caspase-9 and -3, resulting in apoptosis. Exposure to LAQ824 decreased Bcr-Abl, p-(phosphor) AKT, p-ERK1/2 and Bcl-xL levels in CML-BC cells. LAQ824 treatment also increased the mRNA and protein expressions of the death receptors DR5 and/or DR4, but reduced the mRNA and protein levels of c-FLIP. As compared to treatment with Apo-2L/ TRAIL (100 ng/ml) or LAQ824 alone, pre-treatment with LAQ824 increased the assembly of FADD and caspase-8, but not of c-FLIP, into the Apo-2L/TRAIL-induced death inducing signaling complex (DISC). This was associated with increased processing of caspase-8 followed by BID, cytosolic accumulation of the pro-death molecules cytochrome-c, Smac and Omi, as well as resulting in increased activity of caspase-3. Treatment with LAQ824 also down regulated the levels of Bcl-2, XIAP and survival. This was not reversed by co-treatment with either a pan-caspase or proteasome inhibitor. Combined treatment with LAQ824 and Apo- 2L/TRAIL induced more apoptosis of the CML-BC and acute leukemia cells than either agent alone ($p<0.05$). Partial inhibition of apoptosis exerted by Bcl-2 over-expression was reversed by co-treatment with LAQ824 and Apo-2L/ TRAIL. Significantly, co-treatment with LAQ824 and Apo-2L/TRAIL induced more apoptosis of primary AML and CML-BC blast samples than either agent alone ($p<0.05$). Taken together, these findings indicate that LAQ824 increases not only Apo-2L/TRAIL-induced DISC activity, but also down-modulates the levels of Bcr-Abl and mitochondria-based Bcl-2 and Bcl-xL as well as the down stream XIAP and survivin. These modulations due to LAQ824 treatment lower the threshold for Apo-2L/TRAIL-induced apoptosis of human CML-

BC and acute leukemia cells. These studies clearly highlight the promising pre-clinical anti-leukemia activity and its mechanistic basis, of the combination of LAQ824 and Apo-2L/ TRAIL.

L70 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:441944 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300441944
TITLE: Co-treatment with histone deacetylase inhibitors suberoylanilide hydroxamic acid (SAHA) enhances Apo-2L/TRAIL -induced death inducing signaling complex and apoptosis of human acute lymphoid leukemia cells.
AUTHOR(S): Guo, Fei [Reprint Author]; Tao, Jianguo [Reprint Author]; Wittmann, Sylvie [Reprint Author]; Bali, Purva [Reprint Author]; Bhalla, Kapil N. [Reprint Author]
CORPORATE SOURCE: H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 154. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003

L70 ANSWER 12 OF 12 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:368086 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300368086
TITLE: Co-Treatment with the Histone Deacetylase Inhibitor Suberoylanilide Hydroxamic Acid (SAHA) Enhances Apo-2L/TRAIL-Induced Death Inducing Signaling Complex and Apoptosis of Human Acute Lymphoid Leukemia Cells.
AUTHOR(S): Fei, Guo [Reprint Author]; Wittmann, Sylvie [Reprint Author]; Richon, Victoria [Reprint Author]; Bhalla, Kapil [Reprint Author]
CORPORATE SOURCE: Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 4602. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 2003
Last Updated on STN: 18 Sep 2003

AB SAHA (Suberoylanilide hydroxamic acid) is a known inhibitor of histone deacetylases (HDACs), which catalyze deacetylation of amino terminal lysine residues of the core nucleosomal histones, an activity implicated in chromatin remodeling and the transcriptional regulation of cell-cycle and differentiation regulatory genes, e.g., p21 and p27. Previous studies from our laboratory have demonstrated that human acute leukemia cells express death receptor DR5 and are sensitive to Apo-2L/TRAIL-induced death inducing complex (DISC) and apoptosis. In the present studies we determined the effect of exposure to SAHA on the expression of DR5, as well as on Apo-2L/TRAIL-induced DISC and apoptosis of B lymphoblast SKW6.4 and Jurkat T leukemia cells. Treatment with SAHA (2.0 to 5.0 muM for 24 to 48 hours) significantly increased the mRNA and protein expressions of DR5 and Apo-2L/TRAIL, as determined by a
multi-probe RNase protection assay and immunoblot analyses, and induced apoptosis of SKW6.4 and Jurkat cells in a dose dependent manner. This was associated with downregulation of the protein levels of FLIP, XIAP, cIAP1, survivin and Bcl-xL. SAHA treatment induced histone H3 hyperacetylation and p27 expression in SKW6.4 and Jurkat cells, but induced p21 protein levels alone in SKW6.4 cells. In contrast, treatment with SAHA induced cell-cycle G1 phase accumulation of both cell-types. As compared to treatment with SAHA or Apo -2L/TRAIL (100 ng/ml for 24 hours) alone, co-treatment with SAHA and Apo-2L/TRAIL (for 24 hours) induced significantly more PARP-cleavage activity of caspase-3 and apoptosis of SKW6.4 and Jurkat cells ($p<0.05$). This was associated with significantly increased recruitment of FADD and caspase-8 into Apo-2L/TRAIL-induced DISC, incorporating oligomerized DR5. Apoptosis induced by SAHA and/or Apo-2L/TRAIL was
significantly inhibited by co-treatment with DR5:Fc ($p<0.05$), indicating that SAHA-induced expression of Apo- 2L/TRAIL and DR5 were mechanistically involved in SAHA-induced apoptosis of SKW6.4 and Jurkat cells. Taken together, these findings indicate that treatment with SAHA induces the expression of DR5 and Apo-2L/
TRAIL, as well as sensitizes human lymphoid leukemia cells to Apo-2L/TRAIL-induced DISC and apoptosis. They also suggest that co-treatment with SAHA and Apo- 2L/TRAIL may be a promising therapeutic strategy that should be tested against human acute lymphoid leukemia.

FILE 'HOME' ENTERED AT 16:26:57 ON 19 AUG 2008

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=> d his ful

     FILE 'REGISTRY' ENTERED AT 14:53:34 ON 19 AUG 2008
L1      4222979 SEA ABB=ON  PLU=ON  ?HYDROXY?/CNS
L2       259102 SEA ABB=ON  PLU=ON  ?PROPENAMIDE?/CNS
L3       262916 SEA ABB=ON  PLU=ON  ?"INDOL-3-YL"?/CNS
L4          711 SEA ABB=ON  PLU=ON  L1(L)L2(L)L3
                E "APO-2L"/CN
                E TRAIL/CN
L5           12 SEA ABB=ON  PLU=ON  (TRAIL/CN OR "TRAIL (TUMOR NECROSIS
                FACTOR-RELATED APOPTOSIS-INDUCING LIGAND) (52-ASPARAGINE,
                82-GLUTAMINE) (HUMAN)"/CN OR "TRAIL (TUMOR NECROSIS
                FACTOR-RELATED APOPTOSIS-INDUCING LIGAND) (HUMAN FRAGMENT)"
                /CN OR "TRAIL RECEPTOR 1/TR4 (HUMAN)"/CN OR "TRAIL
                RECEPTOR 2 (HUMAN CELL LINE NTERA-2)"/CN OR "TRAIL
                RECEPTOR 2 (HUMAN GENE DR5)"/CN OR "TRAIL RECEPTOR 2/TR7
                (HUMAN)"/CN OR "TRAIL RECEPTOR 3 (HUMAN)"/CN OR "TRAIL
                RECEPTOR 3/TR5 (HUMAN)"/CN OR "TRAIL RECEPTOR 4/TR10
                (HUMAN)"/CN OR "TRAIL RECEPTOR APO-2 (357-LEUCINE) (HUMAN
                CLONE 27868 PRECURSOR)"/CN OR "TRAIL RECEPTOR APO-2
                (357-METHIONINE) (HUMAN CLONE 27868 PRECURSOR)"/CN)

     FILE 'HCAPLUS' ENTERED AT 14:56:14 ON 19 AUG 2008
L6             9 SEA ABB=ON  PLU=ON  (HYDROXY(S)INDOL?)(S)(2(W)PROPENAMIDE)

     FILE 'REGISTRY' ENTERED AT 14:58:04 ON 19 AUG 2008
                E HISTONE DEACETYLASE/CN
L7           195 SEA ABB=ON  PLU=ON  HISTONE DEACETYLASE?/CN
                E HISTONE DEACETYLASE INHIBITOR/CN

     FILE 'HCAPLUS' ENTERED AT 14:58:46 ON 19 AUG 2008
                SET REN ON
L8         12435 SEA ABB=ON  PLU=ON  L4 OR L6 OR L7 OR HDAI OR HDAC OR HDI
                OR HISTONE(W)(DEACETYLASE OR DE ACETYLASE)
L9         32923 SEA ABB=ON  PLU=ON  L5 OR DR4 OR DR5 OR (DECOY OR DEATH)(W)
                RECEPTOR OR DCR2 OR DCR 2 OR TRAIL OR APO2L OR APO2 OR
                (APO OR APOPTOS? OR APOPTOT?)(W)(2 OR 2L) OR AGONIST?(3A)AN
                TIBOD? OR (TNF OR (TUMOUR OR TUMOR)(W)NECROSIS)(5A)(LIGAND
                OR SUPERFAMIL? OR SUPER FAMIL? OR RECEPTOR)
L10          136 SEA ABB=ON  PLU=ON  L8(L)L9
L11       261058 SEA ABB=ON  PLU=ON  (TREAT? OR THERAP? OR PREVENT?)(S)((PRO
                LIFERAT? OR PRO LIFERAT?)(3A)(DISEAS? OR DISORDER) OR
                ?CANCER? OR ?CARCIN? OR ?TUMOUR? OR ?TUMOR? OR ?NEOPLAS?)
                E CYTOKINE RECEPTORS+ALL/CT
L12          8819 SEA ABB=ON  PLU=ON  "CYTOKINE RECEPTORS"+OLD/CT
                E ANTIBODIES+ALL/CT
                E E2+ALL
L13       318585 SEA ABB=ON  PLU=ON  "ANTIBODIES AND IMMUNOGLOBULINS"+OLD,PF
                T/CT
L14          478 SEA ABB=ON  PLU=ON  L8 AND (L13 OR L12)
L15          353 SEA ABB=ON  PLU=ON  L14 AND HUMAN/CT
                E ANTITUMOR AGENTS+ALL/CT
L16       272881 SEA ABB=ON  PLU=ON  "ANTITUMOR AGENTS"+OLD,PFT/CT
                E NEOPLASM+ALL/CT
L17       193859 SEA ABB=ON  PLU=ON  NEOPLASM+OLD,PFT/CT
                E LEUKEMIA+ALL/CT
L18        41140 SEA ABB=ON  PLU=ON  LEUKEMIA+OLD,PFT/CT
                E ACUTE MYELOID LEUKEMIA+ALL/CT
L19         9985 SEA ABB=ON  PLU=ON  "ACUTE MYELOID LEUKEMIA"+OLD,PFT/CT
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                E "DISEASE, ANIMAL"+LT/CT
                E E104+ALL
L20          2538 SEA ABB=ON  PLU=ON  "DISEASE, ANIMAL (L) PROLIFERATIVE"+OLD
                ,PFT/CT
L21           219 SEA ABB=ON  PLU=ON  L15 AND ((L16 OR L17 OR L18 OR L19 OR
                L20))
                E SIGNAL TRANSDUCTION+ALL/CT
L22        199042 SEA ABB=ON  PLU=ON  "SIGNAL TRANSDUCTION"+OLD,PFT/CT
                E CYCLIN DEPENDENT KINASE INHIBITORS+ALL/CT
L23         16484 SEA ABB=ON  PLU=ON  "CYCLIN DEPENDENT KINASE INHIBITORS"+PF
                T/CT
                E APOPTOSIS+ALL/CT
L24        125051 SEA ABB=ON  PLU=ON  APOPTOSIS+OLD,PFT/CT
L25           136 SEA ABB=ON  PLU=ON  L21 AND ((L22 OR L23 OR L24))
                D KWIC
                D QUE
L26         75920 SEA ABB=ON  PLU=ON  (L12 OR L13) AND HUMAN/CT
L27         18430 SEA ABB=ON  PLU=ON  L26 AND ((L16 OR L17 OR L18 OR L19 OR
                L20))
L28          3249 SEA ABB=ON  PLU=ON  L27 AND ((L22 OR L23 OR L24))
L29          2886 SEA ABB=ON  PLU=ON  L28 AND THU/RL
L30          1307 SEA ABB=ON  PLU=ON  L8(L)((L16 OR L17 OR L18 OR L19 OR
                L20))
L31           937 SEA ABB=ON  PLU=ON  L30 AND HUMAN/CT
L32            95 SEA ABB=ON  PLU=ON  L8(L)(L12 OR L13)
L33            62 SEA ABB=ON  PLU=ON  L32 AND ((L16 OR L17 OR L18 OR L19 OR
                L20))
L34            54 SEA ABB=ON  PLU=ON  L33 AND HUMAN/CT
L35            51 SEA ABB=ON  PLU=ON  L34 AND THU/RL
L36            30 SEA ABB=ON  PLU=ON  L35 AND ((L22 OR L23 OR L24))
L37             1 SEA ABB=ON  PLU=ON  US2007-571734/AP
L38        274695 SEA ABB=ON  PLU=ON  (TREAT? OR THERAP? OR PREVENT?)(S)((PRO
                LIFERAT? OR PRO LIFERAT?)(3A)(DISEAS? OR DISORDER) OR
                ?CANCER? OR ?CARCIN? OR ?TUMOUR? OR ?TUMOR? OR ?NEOPLAS?
                OR AML OR LEUKEMI## OR LEUKAEMI##)
L39            77 SEA ABB=ON  PLU=ON  L10(L)L38
L40            31 SEA ABB=ON  PLU=ON  L39(L)(MAMMAL? OR HUMAN)
L41            91 SEA ABB=ON  PLU=ON  L21 AND L24
L42            30 SEA ABB=ON  PLU=ON  L41 AND (L22 OR L23)
L43            30 SEA ABB=ON  PLU=ON  L42 AND HUMAN/CT
L44            30 SEA ABB=ON  PLU=ON  L43 AND THU/RL

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED
     AT 15:35:02 ON 19 AUG 2008
L45           114 SEA ABB=ON  PLU=ON  L40

     FILE 'REGISTRY' ENTERED AT 15:42:41 ON 19 AUG 2008
                E "CASPASE-8"/CN 5
L46            14 SEA ABB=ON  PLU=ON  "CASPASE-8"?/CN

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED
     AT 15:44:10 ON 19 AUG 2008
L47            32 SEA ABB=ON  PLU=ON  L45(L)(L46 OR (CASP OR CASPASE)(1W) 8
                OR FLICE OR (MACH OR MCH5 OR MCH 5)(3A)(PROTEASE OR
                PROTEINASE))

     FILE 'HCAPLUS' ENTERED AT 15:45:36 ON 19 AUG 2008
L48            11 SEA ABB=ON  PLU=ON  L44 AND (L46 OR (CASP OR CASPASE)(1W)8
                OR FLICE OR (MACH OR MCH5 OR MCH 5)(3A)(PROTEASE OR
                PROTEINASE))
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     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED
     AT 15:49:37 ON 19 AUG 2008
L49           0 SEA ABB=ON  PLU=ON  L43

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED
     AT 15:57:16 ON 19 AUG 2008
L50          15 DUP REM L47 (17 DUPLICATES REMOVED)
L51          60 DUP REM L45 (54 DUPLICATES REMOVED)
L52         598 SEA ABB=ON  PLU=ON  L8 AND L9
L53         363 SEA ABB=ON  PLU=ON  L52 AND L38
L54         105 SEA ABB=ON  PLU=ON  L53 AND (L46 OR (CASP OR CASPASE)(1W)
                8 OR FLICE OR (MACH OR MCH5 OR MCH 5)(3A)(PROTEASE OR
                PROTEINASE))
L55          96 SEA ABB=ON  PLU=ON  L54 AND (MAMMAL? OR HUMAN)
L56          96 SEA ABB=ON  PLU=ON  L47 OR L55
L57          59 DUP REM L56 (37 DUPLICATES REMOVED)

     FILE 'HCAPLUS' ENTERED AT 16:07:05 ON 19 AUG 2008
L58          39 SEA ABB=ON  PLU=ON  L40 OR L48
                D QUE L40
                D QUE L48
                D L58 1-39

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS' ENTERED
     AT 16:09:12 ON 19 AUG 2008
                D QUE L47
                D QUE L49
                D QUE L55
                D L57 1-59 IBIB ABS

     FILE 'MEDLINE' ENTERED AT 16:09:42 ON 19 AUG 2008
                E "RECEPTORS, TNF-RELATED APOPTOSIS"+ALL/CT
                E E4+ALL
L59         736 SEA ABB=ON  PLU=ON  ("RECEPTORS, TNF-RELATED APOPTOSIS-INDU
                CING LIGAND"/CT OR D12.776.543.750.705.852.760.396./CT OR
                D12.776.543.750.73.600./CT)
                E  HISTONE DEACETYLASES+ALL/CT
L60        4831 SEA ABB=ON  PLU=ON  ("HISTONE DEACETYLASES"/CT OR D8.811.27
                7.87.520./CT)
L61        2410 SEA ABB=ON  PLU=ON  L60(L)AI/CT
L62          13 SEA ABB=ON  PLU=ON  L59 AND L61
                D QUE
                D 1-13

     FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PASCAL, DISSABS'
     ENTERED AT 16:20:06 ON 19 AUG 2008
L63         284 SEA ABB=ON  PLU=ON  "ATADJA P"?/AU
L64        1108 SEA ABB=ON  PLU=ON  "BHALLA K"?/AU
L65          77 SEA ABB=ON  PLU=ON  L63 AND L64
L66          94 SEA ABB=ON  PLU=ON  ((L63 OR L64 OR L65)) AND L9
L67          24 SEA ABB=ON  PLU=ON  L66 AND L8
L68           3 SEA ABB=ON  PLU=ON  ((L63 OR L64 OR L65)) AND L21
L69          25 SEA ABB=ON  PLU=ON  L67 OR L68
L70          12 DUP REM L69 (13 DUPLICATES REMOVED)
                D 1-12 IBIB ABS

     FILE 'HOME' ENTERED AT 16:26:57 ON 19 AUG 2008
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FILE HOME

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 AUG 2008 HIGHEST RN 1041768-00-6
DICTIONARY FILE UPDATES: 18 AUG 2008 HIGHEST RN 1041768-00-6

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FILE MEDLINE
FILE LAST UPDATED: 16 Aug 2008 (20080816/UP). FILE COVERS 1949 TO DA

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See HELP RANGE before carrying out any RANGE search.

FILE BIOSIS
FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 13 August 2008 (20080813/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926 through 1968. These records have been re-indexed to match current BIOSIS indexing.

FILE EMBASE
FILE COVERS 1974 TO 19 Aug 2008 (20080819/ED)

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EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

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FILE LAST UPDATED: 15 AUG 2008 <20080815/UP>
MOST RECENT UPDATE: 200852 <200852/DW>
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ECLA reclassifications to June and US national classifications to the end of April 2008 have also been loaded. Update dates 20080401 and 20080701/UPEC and /UPNC have been assigned to these.

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FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomsonreuters.com/support/patents/coverage/latestup

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FILE JAPIO
FILE LAST UPDATED: 8 JUL 2008 <20080708/UP>
MOST RECENT PUBLICATION DATE: 27 MAR 2008 <20080327/PD>

>>> GRAPHIC IMAGES AVAILABLE <<<

FILE PASCAL
FILE LAST UPDATED: 18 AUG 2008 <20080818/UP>
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